

ANNALS of SURGERY

A MONTHLY REVIEW OF SURGICAL SCIENCE AND PRACTICE

ALSO THE OFFICIAL PUBLICATION OF THE AMERICAN SURGICAL ASSOCIATION; THE SOUTHERN SURGICAL ASSOCIATION; PHILADELPHIA ACADEMY OF SURGERY; NEW YORK SURGICAL SOCIETY.



VOLUME 125
JANUARY-JUNE
1947

EDITORIAL BOARD

JOHN H. GIBBON, JR., M.D. <i>Chaitman, Philadelphia. Pa.</i>	WALTER E. LEE, M.D. <i>Philadelphia, Pa.</i>
BARNEY BROOKS, M.D. <i>Nashville, Tenn.</i>	ROY D. McCLURE, M.D. <i>Detroit, Mich.</i>
E. D. CHURCHILL, M.D. <i>Boston, Mass.</i>	H. C. NAFFZIBER, M.D. <i>San Francisco, Calif.</i>
EVARTS A. GRAHAM, M.D. <i>St. Louis, Mo.</i>	D. B. PHEMISTER, M.D. <i>Chicago, Ill.</i>
ROSCOE R. GRAHAM, M.D. <i>Toronto, Canada</i>	W. F. RIENHOFF, M.D. <i>Baltimore, Md.</i>
SAMUEL C. HARVEY, M.D. <i>New Haven, Conn.</i>	A. O. WHIPPLE, M.D. <i>New York, N. Y.</i>

Copyright, 1947
by J. B. Lippincott Company

PRINTED IN U. S. A.

CONTRIBUTORS TO VOLUME 125

ABBOTT, KENNETH H., M. D., Rochester, Minn.			
ABRAMSON, DAVID I., Maj., M. C., A. U. S., Galesburg, Ill.	608	HORSLEY, GUY W., M. D., Richmond, Va.	703
ALLBRITTEN, FRANK R., Jr., Maj., M. C., A. U. S., Philadelphia, Pa.	203	HOWORTH, M. BECKETT, M. D., New York, N. Y.	
BALR, RUDOLF L., M. D., New York, N. Y.	418	HYMAN, JACK, M. D., New Orleans, La.	216
BARGIN, J. ARNOLD, M. D., Rochester, Minn.	115		788
BARTELS, ELMER C., M. D., Boston, Mass.	572	KANOR, ABRAM, M. D., New York, N. Y.	418
BARTLETT, WILLARD, M. D., St. Louis, Mo.	566	KITTREDGE, W. E., M. D., New Orleans, La.	788
BAXTER, HAMILTON, M. D., Montreal, Quebec, Canada		KLLME, ROLAND M., M. D., St. Louis, Mo.	49
BECKER, WALTER F., M. D., Charlottesville, Va.	177	KRONIRIS, A., Maj., Athens, Greece	505
BLARRY, ROBERT E. L., M. D., Ann Arbor, Mich.	515	KROKINA, N. A., M. D., Leningrad, U S S R.	241
BLAINE, GEORGE, Maj., R. A. M. C., Sutton, Surrey, England	729	LADD, WILLIAM E., M. D., Boston, Mass.	23
BLALOCK, ALFRED, M. D., Baltimore, Md.	102	LAHEY, FRANK H., M. D., Boston, Mass.	572
BRADLEY, CLOYCE F., M. D., Nashville, Tenn.	129	LAM, CONRAD R., M. D., Detroit, Mich.	658
BURCH, JOHN C., M. D., Nashville, Tenn.	768	LANCOHR, JOHN L., M. D., Boston, Mass.	452
BURNS, EDGAR, M. D., New Orleans, La.	788	LE BLOND, CHARLES P., M. D., Columbus, Ohio	25
CAMPBELL, KENNETH N., M. D., Ann Arbor, Mich.		LEHMAN, EDWIN P., M. D., Charlottesville, Va.	51
CAVE, EDWIN F., M. D., Boston, Mass.	729	LIVINOSTON, KENNETH E., Lt., M. C. (S), U. S. N. R., Boston, Mass.	431
CLARK, JOHN H., M. D., New Orleans, La.	126	LONG, JOHN C., M. D., New York, N. Y.	89
COLEMAN, CLAUDE C., M. D., Richmond, Va.	718	LORIAN, PAUL H., M. D., Kansas City, Kan.	171
COLLER, FREDERICK A., M. D., Ann Arbor, Mich.		LYONS, CHAMP, M. D., New Orleans, La.	618
COLONNA, PAUL C., M. D., Philadelphia, Pa.	729	LYONS, RICHARD H., M. D., Ann Arbor, Mich.	729
COPF, OLIVER, M. D., Boston, Mass.	96	MAHONEY, E. B., M. D., Rochester, N. Y.	590
CRAIG, WINCHELL MCK., M. D., Rochester, Minn.	1, 452	MARSHALL, SAMUEL F., M. D., Boston, Mass.	
CROCE, EDMUND J., Maj., M. C., A U. S., Staten Island, N. Y.	608	MARTIN, J. D., Jr., M. D., Atlanta, Ga.	688
CURTIS, GEORGE M., M. D., Columbus, Ohio	349	MARTIN, JOHN, M. D., Chicago, Ill.	756
DAVIS, LOYAL, M. D., Chicago, Ill.	647	MAYERSON, H. S., Ph. D., New Orleans, La.	618
DEBAKEY, MICHAEL, M. D., New Orleans, La.	522	MCCLURE, ROY D., M. D., Detroit, Mich.	658
DECAMP, PAUL, M. D., New Orleans, La.	618	MCFEER, GORDON, M. D., New York, N. Y.	89
DIXON, LEONARD, M. D., New Orleans, La.	522	MERKEL, WALTER C., M. D., Baltimore, Md.	673
ELIASON, E. L., M. D., Philadelphia, Pa.	57	MIDER, G. B., M. D., Rochester, N. Y.	590
FINNEY, GEORGE G., M. D., Baltimore, Md.	673	MILLER, DONALD B., M. D., Baltimore, Md.	673
FIROR, W. M., M. D., Baltimore, Md.	604	MISCALL, LAURENCE, Col., M. C., A. U. S., New York, N. Y.	142, 311
GEY, G. O., M. D., Baltimore, Md.	604	MODLIN, JOHN J., M. D., St. Louis, Mo.	341, 385
GLENN, FRANK, M. D., New York, N. Y.	72	MOE, GORDON K., M. D., Ann Arbor, Mich.	729
GORDON, STUART D., M. D., Toronto, Ontario, Canada	237	MOORE, FRANCIS D., M. D., Boston, Mass.	1
HARE, HUGH F., M. D., Boston, Mass.	688	MORE, ROBERT H., M. D., Montreal, Quebec, Canada	
HARRISON, ALBERT W., Maj., M. C., A. U. S., New York, N. Y.	142, 311	MORTON, JOHN H., M. D., Rochester, N. Y.	177
HARTMAN, J. C., M. D., Philadelphia, Pa.	251	MOSSER, DONN, M. D., Kansas City, Kan.	171
HODGE, IAN G., Maj., M. C., A. U. S., Lancaster, Pa.	399	NELSON, WOODROW, M. D., New Orleans, La.	618
	iii	NEWTON, Z. B., M. D., Philadelphia, Pa.	251
		OCHSNER, ALTON, M. D., New Orleans, La.	522
		OTTO, THOMAS O., M. D., Miami, Fla.	778
		OUTERBRIDGE, RALPH E., M. D., Toronto, Ontario, Canada	282
		OWEN, CORA R., Ph. D., Boston, Mass.	452
		PARKER, JOE M., M. D., St. Louis, Mo.	341, 385
		PRMBERTON, JOHN DEJ., M. D., Rochester, Minn.	

PENICK, RAWLEY M., Jr., M. D., New Orleans, La.	582	SPRINZ, HELMUTH, Maj., M. C., A. U. S., Staten Island, N. Y.	194
PIRRET, GEORGE, M. D., Chicago, Ill.	647	STARK, W. J., Capt., M. C., Vancouver, B. C., Canada	372
PETROV, N. N., M. D., Leningrad, U. S. S. R.	241	STAYMAN, J. W., Jr., M. D., Philadelphia, Pa.	251
POTTLER, STANLEY E., Capt., M. C., A. U. S., Staten Island, N. Y.	349	STEIN, HYMEN D., M. D., New York, N. Y.	89
PULASKI, EDWIN J., Maj., M. C., A. U. S., Staten Island, N. Y.	194	STEWART, CHARLES F., M. D., New York, N. Y.	157
PUPPL, I. DARIN, M. D., Columbus, Ohio	257	SULZBERGER, MARION B., M. D., New York, N. Y.	418
QUIMBY, EDITH H., Sc. D., New York, N. Y.	360	SUTLER, MARTIN R., M. D., Ann Arbor, Mich.	729
RAO, JOHN O., M. D., Detroit, Mich.	249	SWARILLY, W. B., M. D., Philadelphia, Pa.	251
RLMINGTON, JOHN H., M. D., Rochester, Minn.	115	SWEET, RICHARD H., M. D., Boston, Mass.	41
RIENHOFF, WILLIAM F., Jr., M. D., Baltimore, Md.	541	SWENSON, ORVAR, M. D., Boston, Mass.	23
ROWE, CARTER R., M. D., Boston, Mass.	126	TANNA, JEROME F., M. D., New Orleans, La.	80
RUSSEK, HENRY L., M. D., Staten Island, N. Y.	119	TAUBER, ROBERT, M. D., Philadelphia, Pa.	334, 508
SACCOMANNO, GENO, PH. D., St. Louis, Mo.	49	TOCANTINS, LEANDRO M., M. D., Philadelphia, Pa.	292
SALTZSTEIN, HARRY C., M. D., Detroit, Mich.	249	TROLAND, CHARLES E., M. D., Richmond, Va.	718
SANDERS, GEORGE BENTON, Lt. Col., M. C., A. U. S., Louisville, Ky.	399	TYRONE, CURTIS, M. D., New Orleans, La.	669
SCHEMAN, L., Maj., M. C., A. U. S., Brooklyn, N. Y.	510	UTTERBACK, ROBERT A., Lt., M. C., U. S. N. R. St. Louis, Mo.	49
SHAFIROFF, B. G. P., Lt. Col., M. C., A. U. S., Brooklyn, N. Y.	510	WAGNER, FREDERICK B., Jr., M. D., Philadelphia, Pa.	66, 439
SHALLOW, THOMAS A., M. D., Philadelphia, Pa.	66, 439	WARR, RUPERT F., M. D., Toronto, Ontario, Canada	237
SHUMACKER, HARRIS B., Jr., Lt. Col., M. C., A. U. S., Galesburg, Ill.	203	WEBSILR, RICHARD C., Jr., M. D., Boston, Mass.	1
SMITH, BEVERLY C., M. D., New York, N. Y.	360	WEEDEN, WILLIS M., M. D., New York, N. Y.	89
SOUTHWORTH, JAMES L., M. D., Baltimore, Md.	119	WELTY, ROBERT F., M. D., Philadelphia, Pa.	57
		WHITE, J. WARREN, M. D., Greenville, S. C.	662

ANNALS OF SURGERY

VOL. 125

JANUARY, 1947

No. 1



EXPEDITIOUS CARE OF FULL-THICKNESS BURN WOUNDS BY SURGICAL EXCISION AND GRAFTING*

OLIVER COPE, M.D., JOHN L. LANGOHR, M.D.,
FRANCIS D. MOORE, M.D., AND RICHARD C. WEBSTER, JR., M.D.
BOSTON, MASS.

FROM THE DEPARTMENT OF SURGERY OF THE HARVARD MEDICAL SCHOOL AND THE SURGICAL SERVICES AT THE
MASSACHUSETTS GENERAL HOSPITAL, BOSTON.

AT THE TIME of the precipitous entry of the United States into World War II, when burns loomed as an incalculable loss of man power to the Armed Services, review of the burn problem suggested that changes in the surgical handling of the burn patient must be introduced. Considering the suddenness with which a limited number of trained medical personnel might be overwhelmed by a large number of burn casualties under conditions of warfare, too much time and attention were lavished on the wound to the neglect of the internal economy of the casualty. There was urgent need for simplification of the wound treatment. From studying the natural history of the burn wound it was found not only that tannic acid as a surface treatment was injurious but also that in burns of partial skin-thickness, which constitute the majority of burn wounds, the best care could be attained by ignoring the wound, except for protecting it with a simple ointment dressing, and abandoning the washing and débriding ritual of the tannic acid method. Experience with this simplified method was obtained under disaster conditions in the care of the victims of the Cocoanut Grove fire.¹ Subsequent experience with such therapy under civilian conditions will be considered in a subsequent paper.²

The simplified therapy of the burn wound, tailored for disaster conditions, introduced no reform in the care of the full-thickness wound. The slough of such a wound was allowed to separate spontaneously or by the aid of wet dressings applied at later dressings. Although invasive infection was usually held in abeyance by chemotherapy, all such full-thickness wounds became infected and it was necessary to linger and await the appearance of healthy granulations before contemplating grafting. By reducing contamination through observance of strict precautions at change of dressings and of maintenance of the optimum nutritional balance, it was feasible to graft some full-thickness wounds at 25 days after injury, but in other patients with more extensive burns, inevitable infection led to debility and the casualty languished for months

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

before all wounds were successfully healed. The full-thickness burn wound emerged during the course of the war as economically and psychologically the most important unsolved problem in the surgical management of the burn patient.

Rehearsal of the life span of the full-thickness burn wound suggested significant differences between it and that of the partial-thickness burn wound other than the absence of viable epithelium. Whereas, in the superficial burn the intact epidermis, even though dead, acts as a protective barrier against the entrance of organisms, in burns where the heat has been of sufficient intensity to cause full-thickness destruction, the epidermis is no longer intact. It is usually cracked or torn and the wound is, therefore, violate. Instead of being bathed by a fluid medium, the more intense heat has coagulated the tissues. Chemotherapeutic agents, able to permeate the wound of partial thickness, are unable to penetrate the coagulum of the full-thickness wound. Such devitalized tissue, devoid of a means of communication with the body fluids, and presumably of a lowered oxygen tension, offers an enticing culture medium to organisms, including the virulent anaerobe. Any counter measures which would intercept infection and lead to expeditious healing must, therefore, include prompt removal of this necrotic tissue. If removal were immediate, and closure of the wound accomplished by grafting, the inevitable contamination of the burn wound would be prevented from developing into an infectious process.

Since the multiplication and invasion of bacterial organisms is rapid, the only means which could possibly eliminate the necrotic tissue before infection develops, is direct surgical excision. The elimination of infection should be accompanied by improved nutrition of the patient and prompt closure of the wound followed by minimal scarring, disability and disfigurement. The early healing should achieve a short period of hospitalization, an economy of manpower and an hopeful outlook by the patient.

The limits of such aggressive surgery suggesting themselves were threatening physiologic imbalance of the patient, a meager amount of donor skin in the extensively burned patient, and inability to recognize with certainty full-thickness destruction of the skin. The physiologic imbalance could be thwarted by prompt and adequate shock therapy, and the quandary over the depth of destruction by increasing experience. The limitations of physiologic imbalance and difficulty of recognizing full-thickness destruction immediately would be exaggerated under conditions of warfare. Under such conditions it might not be possible to maintain adequate physiologic balance or to find the time for scrutiny of the burn wound. Indeed, hospital facilities might be elusive.

The refractoriness of the full-thickness burn has impressed a number of surgeons during the war years. Connor and Harvey, at New Haven, have approached the problem by dissolving the slough chemically. Pyruvic acid starch paste has been found to accelerate the separation of slough, permitting grafting of the area as early as six days after applying the acid.³ Other workers have tried surgical excision of the slough. Young,⁴ in 1942, reported a case, with a burn of 8 to 10 per cent total extent, part of which was excised and grafted three and one-half hours after injury. Ackman, *et al.*,⁵ at Montreal,

have reiterated the importance of expediting the closure of the full-thickness burn wound and have, after surgical excision of the slough, grafted extensive wounds as early as 12 and 16 days following injury. We were privileged to see Gerrie, of this Montreal group, excise the slough of a full-thickness burn wound on the 12th day, with immediate grafting; the take was 80 per cent successful. Gerrie removed the slough by shaving it off with a sharp knife rather than by excision of the wound. Saltonstall and Lee⁶ have reported the grafting of a patient on the 16th day following injury after excising the slough. More recently, McCorkle⁷ has used surgical excision to expedite healing and has reported doing this on the 7th day following injury.

The rationale and theoretic limitations of the program for the expeditious care of full-thickness burn wounds by surgical excision and grafting have been tested. Certain patients received the ideal treatment, that is excision of the full-thickness wound destruction within the first hours after injury, with immediate closure of the wound by split-thickness grafts. Patients in whom physiologic balance was assured were chosen. In other patients, excision of the wound was arbitrarily postponed for a number of days and penicillin administered in that interval in order to see how successful this agent would be in holding invasive infection in abeyance. The initial interval chosen was seven days because it was considered that during this period from injury to excision and grafting it would be feasible for a burn casualty to be dressed and transported from, for example, France to a Base Hospital in England where surgical facilities were available, and physiologic balance of the patient secured. Later this interval was both shortened and lengthened for evaluation of the method.

CLINICAL OBSERVATIONS

The cases of full-thickness burns at this hospital which have been found suitable for early surgical excision and grafting have been divided into three categories according to the extent of the burn and the interval between injury and surgical care. The burns have included those produced by heat, chemicals and electricity. In all, 38 patients with 52 wounds have been so treated.

1. Circumscribed full-thickness burns excised and grafted within the first hours after injury constitute one category. There are ten such cases (Table I), and the report of one, illustrating features of this category, is given:

Case 180.*—Molten magnesium, inadvertently spilled into the shoe of the man while at work, ignited instantaneously, ripping the shoe and burning the side and dorsum of the foot. The patient arrived at this hospital one-half hour later, where examination showed a localized, demarcated burn (Plate I A). The burned skin consisted of a white, slightly gelatinous coagulum without sensation or visible sign of circulation. Bordering the white coagulum, and in contrast to it, was a tender zone of intense pink of dilated small vessels which blanched with pressure and became pink again immediately upon release of the pressure. This zone with active circulation is seen in Plate I A along the plantar margin of the burn.

* The same case numbers are used in all articles on burn patients studied at this hospital under contract with the Committee on Medical Research. Numbers 1 through 39 refer to the Cocoanut Grove fire cases; numbers 40 through 96 to cases studied before the Cocoanut Grove fire; and numbers 97 through 278 to cases studied since the Cocoanut Grove fire.

TABLE I

CIRCUMSCRIBED FULL-THICKNESS BURNS IMMEDIATELY EXCISED AND GRAFTED

Case No. Sex Age (Yr.)	Site of Wound	Wound Extent Per Cent		Time-Hours Injury to Excision	Operative Shock and Treatment	Result Graft Take Per Cent	Reason for Failure	Time-Days Injury to Healing	Time-Days Injury to Discharge
		Total	3°						
162 F 13	Rt. foot	1	1	5	None None	99	Suture line Loss	14	18
174 M 17	Lt. wrist	1	0.5	4	None None	100		11	12
175 M 34	Scalp, neck Lt. forearm	1.5	0.5	3	None None	100 ¹		10	5
180 M 35	Lt. foot	1.5	1.5	6	None None	100		14	39
192 F 39	Lt. arm and hand	3	3	8	None None	95	Suture line loss	25	18
225 F 54	Lt. arm Lt. shoulder	3.5	3	53 ²	None 500 cc. W. blood	75	Poor immobili- zation ³	75	71
240 M 5	Rt. leg	1.75	1.5	4.25	None 100 cc. plasma 250 cc. W. blood	95	Suture line loss Hematoma	19	19
248 ⁴ M 62	Rt. forearm Rt. hand	10	3	11	None 500 cc. W. blood 250 cc. plasma	95	Sepsis Refrigeration of donor skin	40	47
253 F 1	Rt. forearm	3	1.5	5	None 150 cc. W. blood	95	Poor immobili- zation	48	48
276 M 60	Rt. forearm	7	1	99	None None	100		27 ⁵	69 ⁶
Average.....								28.3	34.6

¹ Wound edge approximation, no graft (Case 175).² Delayed for tissue sodium studies (Case 225).³ Uncoöperative, mentally retarded epileptic (Case 225).⁴ General anesthesia not used because of burns about face and alcoholic intoxication. Delayed closure necessary because anesthesia used was inadequate for taking donor skin. At 48 hours after excision, grafts were taken but were refrigerated because excision of slough proved inadequate. At 5 days postexcision the base was not compatible with complete closure, the 3-day refrigerated grafts were laid as mosaics (Case 248).⁵ Healing of wound delayed because of incomplete excision of full-thickness destruction at one margin (Case 276).⁶ Discharge delayed because of burns of face including eyes (Case 276).

Aware that the skin of the dorsum of the foot is thin, the area of white coagulum was judged to be one of full-thickness destruction. Accordingly, six hours after injury the coagulum was excised under low spinal anesthesia (Plate IB). The excision was carried to the areolar tissue overlying the tendons; the areolar tissue was slightly edematous but judged not killed since the circulation was intact. The wound was closed with a split-thickness graft taken with the dermatome knife from the opposite thigh. The graft was sewn by running suture to the margin of the superficially burned skin (Plate IC). A molded, firm pressure dressing was applied. The patient was given penicillin postoperatively for 19 days. There was no clinical infection, and the take of the graft was complete (Plate ID and E). A circumscribed hematoma dissected its way into one area of the graft, but healing was not intercepted. Use of the foot was started on the 14th day. In order to prevent disruption of the newly formed vascular connections of the graft, an elastic bandage was applied whenever the foot was below the horizontal, and walking was intermittent and only gradually increased.

The burn site and extent,* the interval from injury to closure of the

* The total and full-thickness extents of the body surface burned are computed according to the Berkow scale.⁸

wound, and the results in the ten cases with circumscribed full-thickness burns are summarized in Table I. The anesthetic and chemotherapy used, duration of operation, and bacteriologic flora encountered are given in the protocol of each case.** The largest area excised and grafted was estimated to be not more than 3 per cent of the body surface. In none of the cases did the total burn, incomplete as well as full-thickness, exceed 10 per cent of the body surface. In half of the patients almost the entire area burned was full-thickness. The areas of the body affected were various; in seven cases the excision and grafting was carried out over superficial tendons of forearm, wrist, lower leg or foot, so-called critical areas. In none was the destruction deeper than the subcutaneous fascia but in all, inspection of the excised tissue left little doubt but that the skin had been completely destroyed.

The operative procedures were carried out between three and 11 hours in eight cases, but not until the 53rd and 99th hours in the other two. The 53-hour delay was necessary in an epileptic (Case 225) who was unable to cooperate; (her burn tissues were also used for radioactive sodium studies). Failure to recognize full-thickness destruction on inspection at entry accounted for the delay in the other (Case 276). Sulfadiazine was given to two patients (Cases 162 and 175) and penicillin to the remainder.

The results are judged to be gratifying and to have been better than in the succeeding categories. The grafts took at least 95 per cent except in one case, that of the epileptic not grafted until the 53rd hour, in whom there was a 25 per cent failure of the initial graft (Case 225). Delay in healing of one wound (Case 276) was occasioned not by incomplete take of the graft but by failure to excise a 0.5-cm. margin of destroyed skin at one point.

Infection developed in two cases, seriously in one, the epileptic. In this latter case, though the infection may have been influenced by the delay in grafting, it was undoubtedly influenced by inadequate immobilization of the grafted areas in an ungovernable patient.

The final healing of the grafted areas has also been pleasing; there is a minimum of scarring, keloid, contractures and disability. The hospitalization and operation disturbed but little the equanimity of the patients. The nutritional status was adequately maintained except in one patient who was a chronic alcoholic (Case 248). The psychologic outlook was good except in the epileptic. The period of hospitalization varied from 5 to 71 days, with an average of 34.6 days. One may question whether chemotherapy had a chance to play a beneficial rôle in this group of patients.

2. Circumscribed full-thickness burns in which excision and grafting were delayed constitute a second category (Table II, 11 patients with 12 wounds). A summary of one case is given as an example:

Case 153.—A 69-year-old, vigorous man was admitted eight days after sustaining a deep burn of the back of a leg. His greasy dungarees caught on fire while he was tending a bonfire. His wound was treated at home by his local physician and wife, a

** A protocol of each patient cited in this and the other papers of this series will be published after the final paper of the series.

TABLE II
CIRCUMSCRIBED FULL-THICKNESS BURNS—EXCISION AND GRAFTING DELAYED BECAUSE OF INVASIVE INFECTION

Case No. Sex Age (Yr.)	Site of Wound	Wound Extent			Time-Days Injury to Admission	Time-Days Admission to Excision	Type of Closure	Operative Shock and Therapy	Result Graft Take Per Cent	Reason for Failure	Time-Days Admission to Healing	Time-Days Admission to Discharge
		Per Cent	3°	0.5								
129 M 72	Lt. leg	0.5	0.5	8	8	Delayed 2 days Complete	Excision: None None Graft: None None	Excision: None None Graft: None None	100		18	31
133 F 53	Lt. thigh	2	1.5	8	4	Immediate Complete	None None	None None	40	Inadequate Immo- bilization Hematoma Trophic changes	97	37
151 M 78	Rt. thigh	12	2	3	6	Immediate Complete	Mild 500 cc. W. blood		95	Sepsis	48	56
152 M 52	Rt. foot	1.5	1	0	18 ¹	Immediate Complete	None None		100		34	55
153 M 69	Lt. thigh Lt. leg	10	9	8	4	Delayed 3 days Complete	Excision: Mild 500 cc. W. blood Graft: None 500 cc. W. blood	Excision: Mild 500 cc. W. blood Graft: None 500 cc. W. blood	95	Incomplete excision Suture line loss Hematoma	47	53
154 M 50	Lt. leg Lt. foot	2	2	2	2	Delayed 2 days Complete	Excision Mild None Graft: None None	Excision Mild None Graft: None None	85	Tension on grafts not optimal Sepsis	43	53
157 M 73	Rt. thigh Rt. leg	6	2.5	18	6	Delayed 2 days Complete	Excision Mild 1000 cc. W. blood Graft None None	Excision Mild 1000 cc. W. blood Graft None None	100		22	127 ²

FULL-THICKNESS BURN WOUNDS

CIRCUMSCRIBED FULL-THICKNESS BURNS—EXCISION AND GRAFTING DELAYED BECAUSE OF INVASIVE INFECTION

TABLE II—Continued

Case No.	Sex	Site of Wound	Wound Extent Per Cent	Time-Days Injury to Admission	Time-Days Admission to Excision	Type of Closure	Operative Shock and Therapy	Result Graft Take Per Cent	Reason for Failure	Time-Days Admission to Healing	Time-Days Admission to Discharge
			Total	3 ^o	0.5	4	5	Delayed 4 days Complete			
182	M	Rt. arm	1.5	1	6	7	Delayed 2 days Complete (by edge approximation)	Excision None None Graft	Inadequate immobilization Sepsis	40	28
206	M	Lt. foot	1.5	0.5	7	7 ³	Delayed 2 days Complete	Excision None None Graft		22	19
212	M	Finger	0.5				Delayed 2 days Complete	Excision None			
							Delayed 2 days Complete	None Graft		18	
							Immediate Complete	None None		21	
								100		18	
								100		7	4
								100		34.5	44

¹ Delay in excision resulted from misjudgment at entry concerning depth of destruction. Should have been treated as patient of first category (Case 152).

² Delay due to infected donor sites (Case 157).

³ Interval ordinarily would have been shorter but was prolonged for surgical treatment of carcinoma of the pharynx (Case 206).

trained nurse, with a petrolatum gauze dressing. No chemotherapy was given. When the presence of infection was recognized he entered the hospital.

Examination on entry disclosed an infected, sloughing, deeply cracked burn covering three-quarters of the dorsum of the left leg and thigh (Plate III A and B). There was also an irregular, narrow margin of partial-thickness destruction with bleb formation. The infection was judged to be invasive because of the irregular character of the inflammation flaring out from the area of deep destruction. Cultures were taken and the patient was started on penicillin systemically.

Four days after entry, when the patient was responding well clinically to hospital care and the visible and palpable inflammation was subsiding (Plate III C and D), the area of full-thickness destruction was excised under low spinal anesthesia. The excision was carried down to the muscles and tendons and included the deep subcutaneous fascia. The wound was dressed with fine-meshed gauze overlaid by rubber tubes for local irrigation of penicillin. Thickly impregnated petrolatum gauze strips were placed over the tubes to form a pocket for the irrigating fluid and a firm outer dressing was applied. For three days the local irrigation of penicillin was added to the systemic.

On the 15th day after injury, the 7th after the start of penicillin administration and the third after excision of the dead tissue, the patient's wound was dressed in the operating room. The invasive infection had disappeared; and the wound base was free of edema and exudate (Plate III E). Firm, minute granulation tufts were appearing here and there, but otherwise the surface was formed essentially of the tissue left after excision. On this healthy base the wound was closed without drainage by placing split-thickness dermatome grafts removed from the abdomen and opposite thigh (Plate III F). The intramuscular administration of penicillin was continued for 24 more days.

The take of the grafts was almost complete. There was necrosis along the margins of an occasional suture line (Plate III G), and over an hematoma (Plate III H). Healing was delayed, however, by failure to recognize and to excise a corner of full-thickness destruction on the medial aspect of the calf (Cf. Plate III D and H). The entire wound was judged closed by the 47th day and the patient was discharged home on the 53rd day. Mobilization was slow and graded; an elastic bandage was applied for the first two months when the leg was dependent. The result has been excellent; function has been good since discharge from the hospital and there is a minimum of residual scar (Plate III I). The patient was dejected on entry to the hospital, fearing that he was going to lose his leg because of his age and the infection. His prompt recovery and subsequent usefulness of his leg have amazed him.

Review of the bacterial flora grown on cultures suggests that penicillin was effective in controlling the invasive infection and did abet the surgery. Five gram-positive organisms grew on the cultures planted on entry, a *beta* and a *gamma* streptococcus, a *Staph. aureus* and two strains of *Cl. welchii*. The first three and one of the last were demonstrated to be penicillin-sensitive *in vitro*. The *Clostridia* disappeared and *E. coli* appeared before excision; the staphylococcus disappeared after excision of the slough.

The observations on the 11 patients of this category (circumscribed full-thickness burns in which excision and grafting were delayed) are summarized in Table II. The details of anesthesia, duration of operation, bacterial flora and chemotherapy are given in the protocols. The areas excised and grafted varied from 2 x 3 cm. to 9 per cent of the body surface, with the total area burned varying from 2 x 3 cm. to 12 per cent. The full-thickness burns included various body areas and, as in the first group, destroyed the subcutaneous fascia but not the deeper tissues. The reason for the delay in excision and grafting in all cases was the presence of active invasive infection. Only one of the cases was admitted on the day of the burn, and the burn of this patient

COLOR PLATES

PLATE IA.—Case 180: The left foot of a 35-year-old man one hour after a burn from molten magnesium. Visible circulation and sensation were absent throughout the white area; full-thickness destruction of the skin was judged to have occurred since the skin in this area is thin. The intact circulation of the adjoining thick plantar skin is shown in the photograph as a rim of intense red. This red zone was hypersensitive.

B.—Case 180: The same site six hours after injury during excision of the white skin assumed to have been fully destroyed. The distal half of the dead skin has already been excised. There was slight edema of the subcutaneous areolar tissue. A tourniquet was not used. The few bleeding points were snapped and tied with silk.

C.—Case 180: The operation completed. The wound left after excision of the dead skin has been closed with a split-thickness graft removed from the opposite thigh.

D.—Case 180: The wound seven days after injury and excision and grafting. There has been a complete take of the graft. Blood, presumably from an unsecured vessel, has dissected its way into the midportion of the graft, discoloring but not preventing the healing of the graft.

E.—Case 180: The wound 44 days after injury and closure. There is slight keloid formation along the margins and in the center of the graft where the hematoma formed.

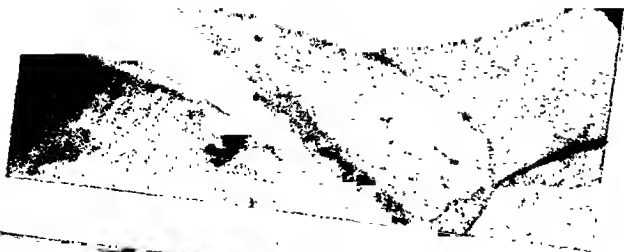
PLATE IIA.—Case 149: Both legs and thighs of a 20-year-old male two hours after sustaining a burn of 72 per cent of the body surface. The skin of the lower legs was firm, white, avascular, asensitive and denuded in part of epidermis; that of the posterior aspect of the thighs was parchment-like. The skin of these areas was considered to have been fully destroyed. The circulation of the skin over both knees was intact and the skin was judged to have been incompletely damaged.

B.—Case 149: Both legs and thighs from the left side on the day of injury. The left leg was judged to have received more extensive full-thickness destruction and was selected for surgical care on the 7th day. It was wrapped in petrolatum gauze without débridement. (The right leg was wrapped in pyruvic acid paste.)

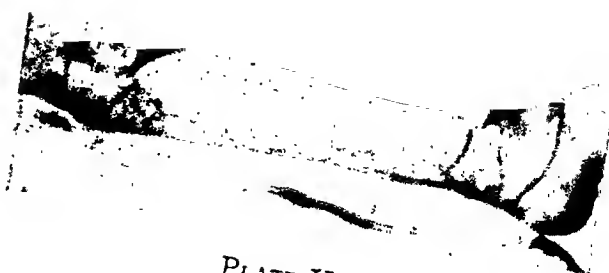
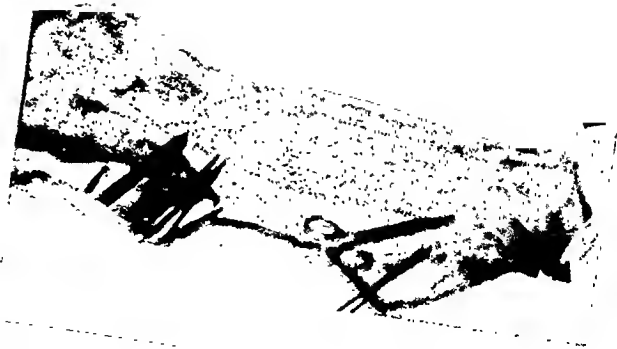
C.—Case 149: Medial aspect of the left leg seven days after injury and immediately before surgical excision of the slough and grafting.

D.—Case 149: Medial aspect of left leg during excision of the dead skin. The vital skin around the knee with intact circulation is being saved. No tourniquet is being used.

E.—Case 149: Medial aspect of left leg immediately following closure with a stocking of split-thickness grafts removed from the anterior chest and abdomen, the only unburned portions of the body.



B



E

PLATE I

PLATE II

PLATE II F.—Case 149: Lateral aspect of the left leg seven days after injury and immediately before surgical excision of the slough and grafting.

G.—Case 149: The popliteal space and posterior aspect of left thigh on the 7th day and prior to excision and grafting.

H.—Case 149: The line of excision of the dead skin on the outer aspect of the left ankle.

I.—Case 149: Excision of the slough of the left leg completed. No tourniquet used.

J.—Case 149: Left leg. Closure of the wound left after excision of slough has been completed by a stocking of grafts.

K.—Case 149: The left leg on the 17th day after grafting, the 24th after injury. There was pressure necrosis around the malleoli and along a few suture lines, otherwise the take of the graft was satisfactory.

L.—Case 149: Posterior aspect of thighs and right leg on the 47th day after injury when postage stamp grafts were placed on the wound areas the slough of which was left to separate spontaneously (left thigh) and with the help of pyruvic acid paste (right thigh and leg).

M.—Case 149: The left leg on the 61st day after grafting, the 68th after injury.

N.—Case 149: The left popliteal space and thigh on the 68th day after injury, failing to reveal at this stage any better healing of the stocking graft which was placed on the excised base than of the later postage-stamp grafts which were placed on the granulating surface.

O.—Case 149: Both legs on the 97th day after injury. Keloid scar has formed diffusely beneath the grafts laid on granulation tissue; contracture is apparent in the popliteal space. In contrast, there is no keloid scarring, except along the suture lines, of the sheet grafts which were laid on the base left after excision; there is no contracture in the popliteal space.

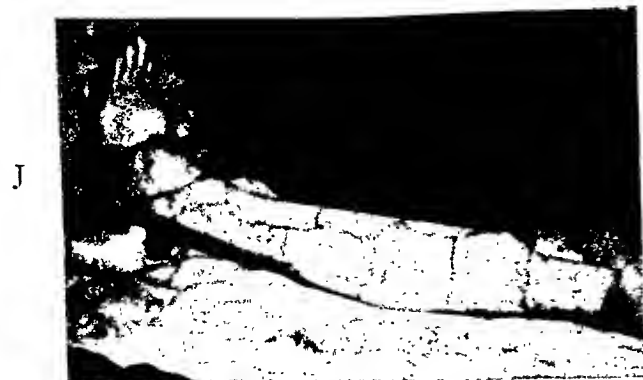
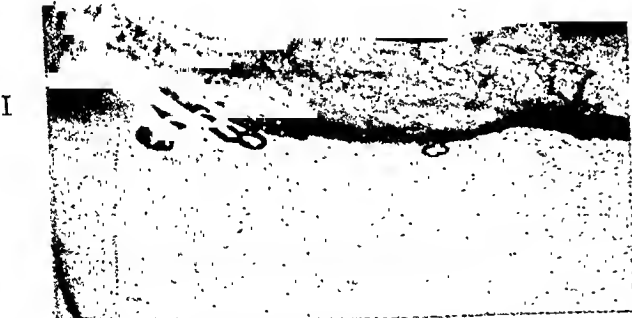
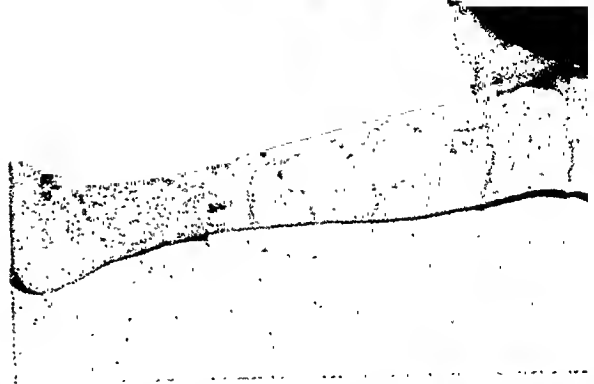
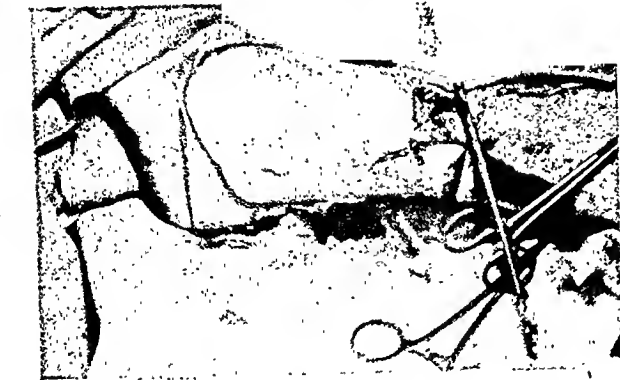
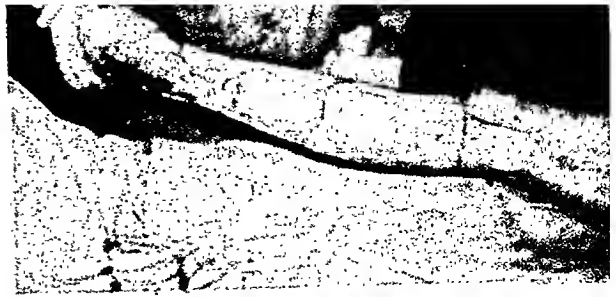


PLATE II (Cont'd.)

PLATE IIIA.—Case 153: Lateral aspect of the left leg of a 69-year-old man on admission to hospital, eight days after injury. The burn, from greasy trousers ignited by a bonfire, had been treated at home with a petrolatum gauze dressing and no chemotherapy. The inflamed irregular border surrounding the deep burn suggested invasive infection.

B.—Case 153: Medial aspect of left leg on day of admission, 8th after injury. The deep infected slough over the calf and popliteal space is to be contrasted with the more anterior incomplete-thickness burn with blebbing.

C.—Case 153: Lateral aspect of left leg on 12th day after injury, 4th day after admission and start of penicillin. The deep burn is more clearly demarcated and the invasive inflammation has decreased.

D.—Case 153: Medial aspect of left leg on 12th day after injury, 4th day after admission and start of penicillin and just before the deep slough was excised.

E.—Case 153: Lateral aspect of left leg on 15th day after injury, 7th after admission and start of penicillin and 3rd after excision of the slough. The tendinous fascia overlying the calf muscles is exposed. All evidence of invasive infection has disappeared. The wound was closed with grafts immediately after this photograph was taken.

F.—Case 153: Medial aspect of left leg immediately following closure of wound with split-thickness grafts on the 15th day after injury, 7th after admission and start of penicillin and 3rd after surgical excision of the slough. An area of doubtful thickness which was not excised is visible in the angle of the wound in the center of this figure.

G.—Case 153: Lateral aspect of left leg on the 7th day after grafting, the 22nd after injury. Except for loss at a few points along the suture line and over a small hematoma, the take of the grafts is complete.

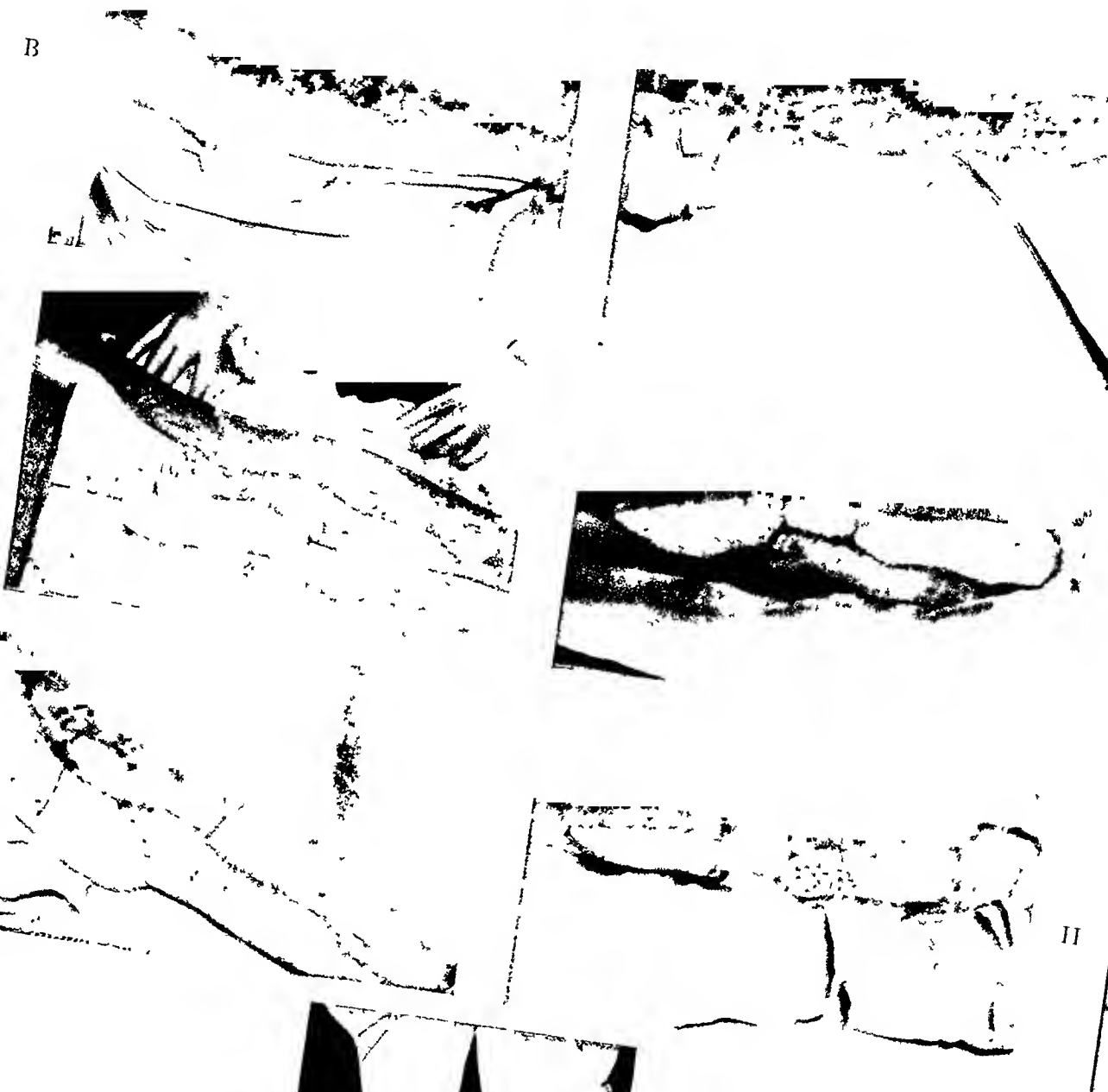
H.—Case 153: Medial aspect of left leg on the 14th day after grafting, the 29th after injury. The failure of the take of the graft caused by the hematoma in the popliteal space and the line of demarcation of the area of questionable full-thickness destruction, which was not excised, are visible.

I.—Case 153: Follow-up of the left leg two years after injury. There is a minimum of scarring and no disability. The grafted skin of the popliteal space was pinched to demonstrate its flexibility.

A

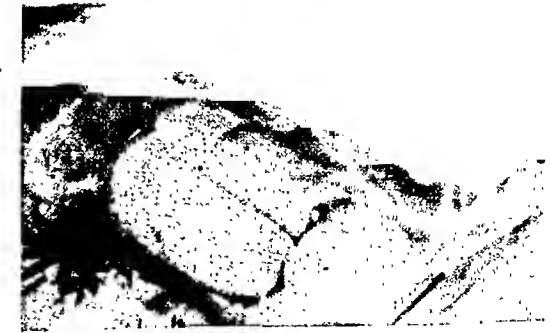
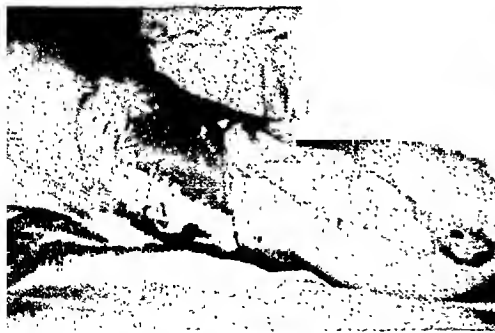


B



I

II



was not immediately excised and grafted because the depth of injury was misjudged on entry to be of only partial skin thickness. The other patients were admitted from two to 18 days after injury.

Because invasive sepsis in all wounds was present at the time excision of the slough was contemplated, chemotherapy in all and delayed closure in the majority were resorted to. Penicillin, either parenterally or locally, was used in all cases, and accompanied by sulfadiazine in two cases (Cases 159 and 206) and tyrothricin in three cases (Cases 152, 153 and 157). A subsidence of the inflammatory reaction was observed in almost all wounds prior to the excision. In four cases the wound was closed immediately following excision. In the other nine an interval of from two to four days was allowed to elapse between excision and closure. In all cases closure was complete. To the excised, ungrafted wounds of the nine cases with delayed closure, penicillin was applied locally.

The results were surprisingly successful. In nine wounds the take of the grafts was virtually complete, a result comparable to the best in the patients of the first category. In the remaining three wounds the takes of the grafts were zero, 40 and 85 per cent. Inadequate tension and immobilization are believed to have accounted for lack of success in the first two of these, and sepsis in the third.

Owing to the clinical observation that the inflammation which was present prior to excision of the burn slough subsided during the parenteral adminis-

PLATE IV A.—Case 135: The right side of the trunk of a 16-year-old girl on entry two hours after a burn from an explosion of a gas stove. The deepest injury, a broad band of parchment-like skin, was outlined by her brassiere.

B.—Case 135: The left side of the trunk at entry. The parchment-like skin extended to the posterior axillary line. The wounds were dressed with petrolatum gauze, without débridement or cleansing. Excision and grafting were planned for the 7th day. Penicillin was started.

C.—Case 135: The slough on chest and abdomen on the 7th day, immediately before the initial excision and grafting. The bluish tint of the slough is from the blue dye, T-1824, used for the plasma volume determinations.

D.—Case 135: The right side and back of the chest on the 7th day, immediately before the initial excision and grafting.

E.—Case 135: The right side of the chest immediately following surgical excision of the slough and closure of the wound with split-thickness grafts. The excision was carried into edematous fat, on which base the grafts were laid.

F.—Case 135: The right side of the chest on the 7th day after excision and grafting, the 14th day after injury. There is sloughing above the suture over the right breast where the excision was incomplete. There are numerous small hematomas in the graft. The take of the graft, however, is complete.

G.—Case 135: The left and unexcised side of the chest on the 14th day after burning. The slough has already separated spontaneously over wide areas; nongranulating inflamed fat is exposed. The wound was excised immediately following the taking of this photograph and a wet penicillin pack dressing applied.

H.—Case 135: The left side of the chest on the 4th day after excision, the 18th after injury. In spite of the inflamed appearance of the base, split-thickness grafts were laid upon it, and the wound closed.

I.—Case 135: The left side of the chest immediately after closure with grafts on the 18th day after injury. The new grafts were sewed to those placed 11 days previously.

J.—Case 135: The left side of the chest on the 7th day after grafting, the 30th after injury. In contrast to the successful take of the grafts on the right side which were placed on the 7th day after injury, the take of these grafts, laid upon an inflammatory base on the 18th day after injury, did not exceed 55 per cent.

tration of chemotherapy, it is hard to escape the conclusion that chemotherapy helped in the successful outcome.

Review of the bacteriologic findings of this group yields evidence that penicillin may have been more effective in certain cases. *B. coli* and *B. proteus* were recovered only from the wounds which did not heal promptly. The recovery of five organisms, all gram-positive, and four penicillin-sensitive *in vitro*, in the case with the most extensive wound in this category, has already been cited in the case report.

The final outcome of the grafting has been varied. Some grafts are excellent, with minimal scarring and producing no disability, while other wounds have formed keloid. It is an impression that the keloid and scarring are roughly proportionate to the amount of the preëxisting infection.

No difficulty in the control of fluid and electrolyte balances or nutrition was encountered in these patients. The dejected psychologic state of some on entry was readily overcome by the promptness of the therapy. The period of hospitalization varied from 4 to 127 days (average 44 days). The time from admission to healing averaged 34.5 days.

3. Extensive full-thickness burns of recent origin constitute the third category in which surgical excision and grafting have been carried out. Thirty wound areas in 17 patients of this category have been so treated.

As an example of the perplexities which may be encountered and the benefits to be derived from prompt therapy, a brief outline is given of the management of the most extensively burned patient of this group in whom early closure was undertaken:

Case 149.—The patient was the driver of a full gasoline truck which, when forced off the road, overturned, caught on fire and exploded. He was extricated by passers-by from the burning cab and thrown into a nearby stream to extinguish his flaming clothing, but not before he had been severely burned. At the community hospital he was given morphine and reached this hospital by ambulance two hours after injury. On entry, it was estimated that 72 per cent of his body surface was burned, 38 per cent of the total surface being full-thickness. The deeper portions were charred and leathery; those of the forehead, ears, upper face, lower neck and over the manubrium, backs of both hands, both lower legs and the backs of both thighs were considered to be full-thickness, while those of the lower back and buttocks, even though tanned, were of questionable depth. The only unburned portions of the body were the lower anterior chest and abdomen.

It was decided to treat the full-thickness burns of one leg by surgical excision and grafting on the 7th day, the wounds to be covered in the meantime with a petrolatum gauze dressing without any débridement or cleansing, and the patient to be given penicillin intramuscularly; pyruvic acid paste, according to the method of Connor and Harvey, was to be applied to the wounds of the other leg. The right leg, the less severely burned of the two (Plate II A and B) was chosen for the pyruvic acid method.

Reasonable homeostasis was achieved and maintained by massive volumes of plasma, saline solution, whole blood and a high protein diet. The details of this therapy are given in the protocol and discussed in later papers under "Disordered Physiology."² Edema of the larynx developed and necessitated tracheotomy at the 30th hour.

Because physiologic equilibrium of the patient and undisturbed renal function were achieved, the operative program could be adhered to. It was hoped that his despondency over his disfigurement would be dissipated by the promise of early healing. On the 7th

day, under intravenous pentothal anesthesia, split-thickness grafts were removed with the dermatome from the entire unburned surface of the anterior chest and abdomen by one operating team while a second team excised the dead hide of the left leg from the ankle to above the popliteal space. Only that amount of full-thickness destruction (12 per cent of the body surface) was excised which could be covered by grafts from the unburned skin available. It was recognized that more of the left thigh would have to be grafted at a later date when skin was again ripe. The wound left after excision was closed by a stocking of grafts and without drainage. Plate II C through J shows the appearance of the necrotic skin before and during excision, the depth of the excision, the nature of the base upon which the grafts were placed and the wound after closure.

The take of the grafts was marred only by pressure necrosis behind the malleoli and Achilles tendon due to a faulty dressing (Plate II K). Separation of the slough of the right leg under the pyruvic acid paste was not prompt (perhaps due to faulty technic of application) and the wounds of this leg and the back of the left thigh were eventually covered on the 47th day by placing mosaic grafts on granulation tissue (Plate II L). The other areas of full-thickness destruction, forehead, face, dorsum of hands and fingers, were also covered by placing grafts on granulations following spontaneous separation of the slough. Each area was grafted as soon as the granulations appeared firm.

The patient responded to the aggressive therapy with excellent morale. He was discharged home, with all wounds closed, on the 85th day after injury and returned to work six weeks after leaving the hospital, or 15 weeks after injury. Cataracts were discernible in both eyes six months after injury, but they have not progressed to the extent of preventing continuous employment.

Follow-up examination showed that the grafts which were laid immediately upon the base left after excision of the slough healed with less scarring and greater mobility than those placed upon fibrous tissue granulations (Plate II M, N and O).

The observations and operations on the 17 patients of this category (recent extensive full-thickness burns) are summarized in Table III. The details of shock and chemotherapy, bacteriology, anesthesia, duration of operation, blood loss, and metabolic observations are given in the protocols, and in many cases also in the articles on bacteriology and disordered physiology.²

The area of full-thickness burns in these patients varied from 1 to 38 per cent and the total burn from 5 to 72 per cent of the body surface. Four of the patients, of whom two were children, had a total burn of less than 10 per cent; they are included in this category of extensive burns because homeostasis was sufficiently disturbed to require postponement of operation. The largest wound area excised and grafted at any one operation was 12 per cent. In some of the wounds in this group, deep structures were burned. The wounds were located in all areas of the body.

The interval between injury and initial operation varied from 1 to 35 days. In some the interval was conditioned by the continued physiologic imbalance of the patient. It was arbitrarily set in many cases on entry in order to explore the usefulness of penicillin in holding infection in the wounds in abeyance, and is longer than would now be practiced. Penicillin was administered intramuscularly from the time of entry to all patients, and locally on some wounds after excision. Sulfamerazine had been given to one patient prior to entry to this hospital (Case 170), otherwise no chemotherapeutic agent other than penicillin was used.

In one-half of the wound areas the grafting was 95 per cent, or more, successful. A few of the wounds excised and grafted after two weeks fall into this excellent group but, in general, the success of grafting diminished with the lengthening of the interval between injury and operation. In all of the areas where grafting failed there were signs of active infection, and the majority of the failures in the group are, therefore, attributed to sepsis. In two of these unsuccessful areas the excision had not been carried deep enough; it is believed that the residual necrotic tissue nourished the infection and prevented the blood supply from succouring the graft.

The decreasing success of grafting with an increasing interval between injury and excision and grafting is impressive; a case from this category of extensively burned patients is cited to illustrate this point:

Case 135.—A 16-year-old girl reached this hospital two hours after her clothes had been ignited by a blast from a gas stove. The front and right side of the trunk and both arms were burned, areas comprising approximately 25 per cent of the body surface. The major portion of the burn was deep. This was believed due to the intensity with which the material of her brassiere burned, for from just to the right of the midline in the back around front to the midaxillary line on the left was a broad, white parchment-like outline of the garment (Plate IV A and B). The lower half of each nipple and of the skin of each breast was included in the parchment-like area. There was also a smaller, irregular zone of white skin on the left side of the abdomen.

The areas of white parchment-like skin were considered to be of full-thickness destruction because visible circulation and sensation were absent. Excision and grafting were planned for the 7th day; the wounds were wrapped in a petrolatum gauze dressing, with no débridement or cleansing, and penicillin was started intramuscularly. Homeostasis was reestablished and held by maintaining a measured, normal circulating blood volume and renal output. On the 7th day the dressings were removed in the operating room. The initial impression of what constituted full-thickness destruction was confirmed; the necrotic tissue was more moist than on entry but no spontaneous separation was yet apparent (Plate IV C and D). Under gas-oxygen-ether anesthesia, the full-thickness portion of the wound of the right side of the chest was excised. The excision was carried into edematous fat; so edematous was the fat posteriorly that small pools of fluid were cut through. On this base were placed six sheets of split-thickness skin removed with the dermatome from the thighs. The wound was closed without drainage by sewing the sheets together and to the borders of the excised wound. The border was made up of the full-thickness slough medially, and elsewhere, of healing second-degree burn (Plate IV E).

On the 7th day after grafting (14th day after injury) the dressings were removed. The take of the grafts was perfect, including those along the margin of the full-thickness burn in the anterior midline. There was slight separation superiorly where the nipple areola and an unexcised margin of skin on the breast had sloughed. Damaged, but doubtful, full-thickness nipple tissue had not been excised on the chance that it might survive (Plate IV F). Spontaneous separation of the unexcised slough on the left side had already started (Plate IV G).

At this second exposure of the wound (14th day after injury) the full-thickness wound of the left side of the chest was excised. In contrast to the edematous fat uncovered seven days previously on the right side, the subcutaneous fat was now inflammatory. It was thickened, stiff, nonwatery, and vascular. In view of this inflammation, presumably infectious in origin, it was decided not to graft immediately but to treat expectantly with a gauze pack and local penicillin in addition to the systemic penicillin. On the 4th day after excision (18th day after injury) the appearance of the base left after excision had

not significantly changed (Plate IV H). In spite of the slight but deep inflammatory reaction, the area was grafted (Plate IV I). The take of the graft, unlike that of the grafting done on the 7th day, was little more than 50 per cent successful.

Undoubtedly, there were factors other than the slowly progressive infectious inflammation beneath the burn of full-thickness which contributed to the partial failure of the take of the 18th day grafting as compared with complete success of the 7th day grafting. The patient had become uncoöperative, had scratched under the dressing, and had torn the grafts near the midline. She was also not eating well and was at the peak of her metabolic and nutritional imbalance. But the presence of all these factors, in addition to progressive sepsis in such a burn wound, only serves to emphasize the importance of closing any full-thickness burn wound immediately.

Clinical signs of infection were encountered in all of the wounds of this category prior to excision, the administration of penicillin, notwithstanding. In one patient the burns of the legs were so deep that tendons and muscles were necrosed, gas gangrene developed and bilateral amputation was necessary.

The final outcome of the grafts has varied considerably. Deep scarring and contractures have formed in those wounds where there was prolonged infection. Good healing, with minimal scar and keloid formation, has taken place in those wounds which were grafted in the first week after injury.

In the care of all of the patients of this category it was necessary to be vigilant concerning burn shock. In some the period of impending shock passed without incident, in others the control of the electrolyte, fluid and plasma colloid balances was not achieved until several days after admission. In many the adaptation to traumatic insult, protein deficit and malnutrition plagued us. In those patients in whom recovery was prompt the initial discouragement was dissipated. The period from injury to discharge from the hospital varied from 22 to 223 days, the average being 87 days (Table III). If the child whose unhealed donor site delayed discharge until the 223rd day is omitted (Case 137), the average becomes 79 days.

TECHNICAL CONSIDERATIONS

The plan of immediate excision and grafting of a full-thickness burn wound will be marred if the surgeon does not appreciate the importance of (1) the assessment of the depth of destruction; (2) chemotherapy as an adjunct; (3) certain details of operative technic (anesthesia, control of hemorrhage, width and depth of excision and the condition of the grafting base); and (4) homeostasis.

1. *Assessment of the Depth of Destruction.*—The surgeon must distinguish the depth of destruction when the patient is first seen in order to treat the full-thickness wounds expeditiously. If the wounds have already been dressed when the patient is seen by the responsible surgeon, the dressings will have to be removed or the surgeon will be blind in his treatment of the wounds and the patient.

The gross appearance of the skin, the state of the circulation and sensation and the position of the burn offer clues for evaluation of the depth of destruction. Charred, tanned, leathery or white, coagulated skin indicates deep destruction. Also, in deeply damaged skin the visible circulation in the small

TABLE III
EXTENSIVE FULL-THICKNESS BURNS EXCISED AND GRAFTED

Case No. Sex Age (Yr.)	Wound Extent Per Cent	Site of Wound	Extent of Excision Per Cent	Time-Days Injury to Excision	Type of Closure	Operative Shock and Treatment	Result Graft Take Per Cent	Reason for Failure	Time-Days Injury to Healing	Time-Days Injury to Discharge
135 F	Total 25 3° 15	Rt. chest Rt. back	9	7	Immediate Complete	Moderate 1000 cc. W. blood	95	Poor immobilization Suture line loss	34	92
16		Lt. chest Upper abdomen	6	14	Delayed 4 days Complete	Excision: Mild 1000 cc. W. blood Graft: Mild 800 cc. W. blood	50	Poor immobilization Sepsis	92	
137 M 6	8	Rt. leg	6	6	Delayed 2 days Complete	Excision: None None Graft: Mild 500 cc. W. blood	65	Incomplete excision Inordinate pressure Sepsis	89	223 ¹
142 M 52	8	1.5 Lt. lat. ankle	0.5	8	Immediate Complete "dermal"	Moderate 500 cc. W. blood	25	Sepsis Hematoma Type of graft	46	
		Lt. lat. calf	0.5		Immediate Complete "epidermal"		85	Sepsis Suture line loss	30	
		Lt. patella	1/8		Delayed 7 days Complete		80	Sepsis	37	123
		Lt. inf. patella	1/8	15	Immediate Complete	None 1000 cc. W. blood	15	Sepsis	60	
		Lt. med. ankle	0.25		Immediate Complete		10	Sepsis	46	
143 M 17	40	Ant. rt. thigh	4	11	Delayed 8 days Complete	Excision: Mild 1000 cc. W. blood	100		32	
		Lt. leg	2	11	Delayed 4 days Complete	1st stage grafting: None	95	Graft overlay bone sequestrum	77	122
			3		Delayed 22 days Complete	500 cc. W. blood 2nd stage grafting: Mild 500 cc. W. blood 3rd stage grafting: Severe Op. discount. 1000 cc. W. blood 250 cc. plasma	80	Hematoma Sepsis	77	

FULL-THICKNESS BURN WOUNDS

TABLE III—Continued
EXTENSIVE FULL-THICKNESS BURNS EXCISED AND GRAFTED

Case No.	Sex	Age (Yr.)	Wound Extent Per Cent	Site of Wound	Extent of Excision Per Cent	Time-Days Injury to Excision	Type of Closure	Operative Shock and Treatment	Result Graft Take Per Cent	Reason for Failure	Time-Days Injury to Healing	Time-Days Injury to Discharge
149	M	20	72	Lt. leg	12	7	Immediate Complete	Mild 1000 cc. W. blood	95	Inordinate pressure	54	85
155	M	48	41	Rt. upper back	8	10	Immediate Complete	Mild 1000 cc. W. blood	75	Tension Sepsis	41	
				Lt. thigh	9		85% delayed 10 days Complete	Excision: Moderate 1000 cc. W. blood	100			
				Lt. leg			15% delayed 30 days Incomplete	1st grafting: 1000 cc. W. blood Severe, (Op. discont.) 2nd grafting: 1000 cc. W. blood	100		62	108
161	M	12	7	Upper back	7		Delayed 14 days Incomplete (Refrig. grafts 14 days)	None	100			
164	M	36	7	Upper back	6.5	5	Immediate Complete	Mild 1000 cc. W. blood	80	Poor immobilization Sepsis	53	60
166	F	30	7.5	Rt. thigh	4	21	Immediate Complete	Moderate 500 cc. W. blood	60	Suture line loss Sepsis	48	60
				Rt. buttock	2.5	31	Delayed 2 days Complete	Excision: None 1000 cc. W. blood	60	Proteolytic sepsis	68	
				Rt. axilla				1000 cc. W. blood Graft. Mild	95	Hematoma Suture line loss	70	
				Rt. breast				1000 cc. W. blood		Unhealed	70	
170	M	15	13	Lt. shoulder	3.5	65-70% Immediate	Excision & 1st grafting: Marked (Op. discont.)	70	Sepsis		29	

TABLE III—Continued
EXTENSIVE FULL-THICKNESS BURNS EXCISED AND GRAFTED

Case No.	Wound Extent		Site of Wound	Extent of Excision Per Cent	Time-Days Injury to Excision	Type of Closure	Operative Shock and Treatment	Result Graft Take Per Cent	Reason for Failure	Time-Days Injury to Healing	Time-Days Injury to Discharge
	Sex	Per Cent									
Age (Yr.)	3°	Total									
42			Lt. arm	2	9	Complete	1000 cc. W. blood	95	Hematoma	66	74
						Delayed 9 days Complete	2nd grafting: None		Suture line loss		
196	15	1	Rt. wrist	1	4	Immediate Complete	None	98	Suture line loss	13	22
M							1000 cc. W. blood				
51							None				
210	31	25	Rt. arm	3	8	Delayed 13 days Incomplete	Excision: Marked (Op. discont.)	100		120	
F			Rt. shoulder				1500 cc. W. blood				128
34			Rt. chest	1.5	8	Delayed 13 days Incomplete	500 cc. plasma	100		102	
							Grafting: Mild				
							1000 cc. W. blood				
218	18	2	Rt. foot	0.25	14	Delayed 3 days Complete	Excision. None	0	Sepsis	62	
M							None				
54							1st grafting: None				114
			Lt. foot	0.25	14	Delayed 15 days Complete	None	60	Sepsis	103	
							2nd grafting. None				
							None				
229	9	7	Rt. shoulder	3.5	31.5	Immediate Complete	None	85	Inadequate immobilization	54	64
F			Rt. breast		(hrs.)		1000 cc. W. blood		Sepsis		
28							500 cc. plasma				
254	45	5	Rt. thigh	0.5	35	Immediate Complete	None	98	Suture line loss	42	64
M							1500 cc. 5% D/W				
38							None				
258	5	1	Lt. shoulder	2x3 cm.	19	Immediate Complete	None	100		26	28
M				3x4 cm.			None				
60											
277	12	11	Rt. leg	11	1	Delayed 2 & 6 days Complete	Excision: None	98		38	45
M							250 cc. W. blood				
6							250 cc. plasma				
							1st grafting: None				
							250 cc. W. blood				
							2nd grafting: None				
							250 cc. W. blood				

vessels is obliterated. Sometimes blood coagulated within the superficial vessels gives the appearance of active circulation but pressure fails to dislodge the pigment. In an incomplete-thickness burn wound with intact circulation not only is the pink color displaced with pressure but the flush returns instantaneously with release of the pressure, so open is the arterial bed.

Sensation is lost if destruction of the skin is complete. Superficial and deep incomplete-thickness burns are usually exquisitely tender except in relatively insensitive areas of the body, such as the buttocks and upper thighs. Careful testing for loss of sensation should be made in all burned areas which are suspected of being of full-thickness.

The location of the burn should be taken into consideration when assessing the depth of skin destruction. Where the skin is normally thin and hair follicles do not extend far beneath the derma, as over the dorsum of the hands and feet, the anterior surface of the wrists, the malar bones of the face and around the eyes, minimal coagulation represents full-thickness destruction. In contrast, charred or leathery skin, without either sensation or visible circulation, does not necessarily indicate full-thickness destruction when it lies over the buttocks, sacral portion of the back, upper portion of the back of the thighs, and in the male over the chin, upper lips and cheeks. The skin of the buttocks, upper thighs and lower back is thick and tough; the hair follicles of the male beard extend well-beneath the derma.

No objective method of determining the depth of destruction of a burn has proven of aid to us. Among other methods we have tried the fluorescent ultra-violet lamp, as suggested by Dingwall⁹ but since it depends upon the presence of the circulation of the blood at a visible level, it has proved no more useful in our hands than the naked eye.

In practice, any quandary over the depth of destruction can be resolved. In a patient with a burn of limited extent, where there is any doubt as to the depth of destruction, it is wise to err by exaggerating rather than depreciating the depth. If the burn is sufficiently deep to be under consideration as one of full-thickness, much time and disability will be saved by excising and grafting it immediately as a full-thickness burn wound. If one waits for the depth to become distinct, the temporizing may tempt the infection and the auspicious moment for getting the wound healed may be lost. Deep incomplete burns, like those of true full-thickness, are so susceptible to infection if the slough is left that much fibrous tissue proliferation in the derma and ugly and disabling scarring will form with spontaneous healing. The condition of the patient with a burn of limited extent should be such to enable him to stand the operation.

In a patient with extensive burns, some of which are of doubtful full-thickness destruction, it is best to depreciate rather than exaggerate the depth of these areas. They will have to be treated, temporarily at least, as of partial-thickness destruction while the veritable full-thickness areas are excised and grafted since the condition of the patient will be such as to enable him to stand just so much surgery and there will be only a meager amount of skin which will be unburned and available for use in grafting. By the time any doubtful

areas prove themselves to be of full-thickness destruction, the condition of the patient should be such as to enable him to stand further surgery, and more healed skin will be available for use in grafting.

2. *Chemotherapy as a Surgical Adjunct.*—Our appraisal of the value of the chemotherapeutic agents, the sulfonamides and penicillin, as adjuncts to the surgical management of full-thickness burn wounds is the result of a clinical impression and a statistical analysis of the bacterial flora cultured. The effect of these agents upon the bacterial flora will be described in a subsequent paper.²

In the partial-thickness burn wound of the skin with blebbing, it was possible to prove free permeation of the sulfonamides into the wound by analyzing the bleb fluid periodically. For as late as five days after injury the concentration of sulfadiazine rose as rapidly in the bleb fluid as in the blood serum following oral administration of the drug.¹⁰ It has not been possible to make such an objective study of the full-thickness wound. The blue dye, T-1824, given intravenously is seen to pass rapidly, within ten minutes, into wounds of partial-thickness but only slowly into deep burns, and then it is found only in the base of the wound. Even after several days the dye has not penetrated far enough through the slough to show at the surface. This dye combines rapidly with the albumin of the serum¹¹ and its passage in the coagulum may well be retarded by the protein. Ionic radioactive sodium, however, requires many hours to enter the burn slough. (The details of the radioactive sodium studies are recounted in a subsequent paper.²) There is indirect bacteriologic evidence suggesting that penicillin does not penetrate the necrotic tissue. Even after prolonged penicillin therapy of high dosage (one to two weeks of 500,000 units per day), the excised slough has been found to contain the same penicillin-sensitive organisms recovered by smear culture at entry. After excision of the slough it has been found possible to eliminate effectively the streptococcus and sometimes the staphylococcus.

From the evidence available, it is suspected that chemotherapeutic agents do not permeate the full-thickness wound to a level comparable to that in the fluid of the partial-thickness wound. Although in neither wound are we sure that the agent enters the damaged cell, in the partial-thickness wound it is in the extracellular space in a therapeutic concentration and may serve to abort the growth of infecting organisms.

Clinical experience bears out the assumption of this difference between the partial- and full-thickness wounds. Infection has proven amenable to control in the partial-thickness wound but ungoverned in the full-thickness. As already stated, all of our full-thickness wounds which were not excised in the first days after inception have become infected in spite of the systemic administration of penicillin or the sulfonamides.

The high incidence of infection in the unexcised full-thickness wound does not mean, however, that penicillin, or the sulfonamides, are without beneficial effect and of no use. The prompt subsidence of invasive infection once penicillin was started in many of the cases in which chemotherapy had been withheld, and the absence of invasive infection in most of the cases in which peni-

cillin was started immediately following injury, indicate that this drug is a valuable adjunct to the surgical management of the deep-burn wound. Only in the cases where the contaminating organisms were not amenable to penicillin or where the depth of tissue destruction was such to damage the blood supply to the limb was invasive infection wholly uncontrolled.

3. *Operative Technic.—Anesthesia:* There is nothing peculiar to burn trauma which has influenced our choice of an anesthetic agent. A normal circulating blood volume and proven normal renal output have been requisites before any anesthetic has been administered. Gas-oxygen-ether, spinal procaine or pantocaine and intravenous pentothal have each been used. In patients with burns of the head and neck we have respected laryngeal edema and have insured an adequate air-way by using an intratracheal tube when administering a general anesthetic.

Control of Hemorrhage: During excision of the burn wound, control of hemorrhage has been arduous. If the excision is carried out in the first 48 hours, during the period of the development of edema, the bleeding is localized to a few arteries which can be easily tied. The edema may persist through the first week but later an inflammatory reaction, presumably the result of spreading infection, develops beneath the burn slough. Where the line of excision is carried into this inflammation, bleeding is profuse, there being many actively bleeding vessels. If the wound is extensive, large volumes of whole blood (as much as 1,750 cc.) may be lost at the time of the excision. It may be impossible to tie all of the small bleeders and control of the hemorrhage is achieved only by prolonged pressure.

In spite of meticulous hemostasis of the excised base immediately before laying the grafts and of applying a pressure dressing over the grafts, an occasional small hematoma has formed. Blood has dissected superficially into the graft, encouraged by the pressure holding the graft in place. Surprisingly, the hematomas have not prevented the successful take of the grafts and have only resulted in transient discoloration.

Width and Depth of Excision: In the excision of full-thickness burn wounds we have committed two technical errors. Failure to excise widely enough has occasioned delay in healing in three patients. We were too conservative in our interpretation of full-thickness destruction. We failed to excise small portions of the wound immediately adjacent to what was known to be full-thickness. Following spontaneous separation of the slough, additional grafts had to be placed to close the wound. In all three cases a little more radical excision could readily have been accomplished.

Failure to excise deeply enough made a secondary grafting procedure necessary in two patients and jeopardized the life of a third because gas gangrene developed in necrotic tissue in two legs not amputated when they should have been. In the first two cases the slough overlay the ankle and there was fear of damaging the tendons to the foot; an adequate excision would have avoided a granulating wound. In the third instance the necrosis involved tendons, muscles and the periosteum of the tibia, and although this deep

necrosis was recognized at the time of excision, we, unwisely, awaited spontaneous demarcation. The development of frank gas gangrene settled the question—débridement was carried out by amputation of both legs.

Grafting Base: The best base upon which to lay grafts is the one left after excision during the first hours after injury. This base may be made up of fatty or areolar tissue, fascia, muscle or periosteum. Even if the base is grossly edematous and exuding water, grafts may be laid directly on it with impunity. The grafts will not take, however, if a thin layer of dead tissue is left, that is, if the excision is not deep enough, or if the base is inflammatory. The longer the delay before excision the greater will be the inflammation.

4. *Homeostasis.*—Homeostasis is precarious in any patient with burns of more than limited extent and it must be effected and maintained not only, as always, to keep the patient alive but also to permit him to go through the surgery required to close his deep wounds promptly and to be in such good condition that his grafted skin will heal. The progress made in achieving homeostasis will be recounted in detail in subsequent papers.² Although the problem of achieving homeostasis early has been made more complicated by the operating attending early excision and grafting, this is more than compensated for later on by the elimination of infection, effecting good nutrition and early healing. We have tried staged operations, thinking that a number of short procedures rather than one long one would prove less insulting. We have no proof that this is generally effective.

DISCUSSION.—It is an extraordinary commentary on the passivity of the surgeon that he has been sitting on the sidelines for so many years watching the full-thickness burn wound degenerate into a bacterial quagmire when the means of healing it promptly by excision and grafting, a simple practice of his art, were at hand.‡ Are there any extenuating circumstances for his passivity? We cannot accept a fear of unseating homeostasis by an operation or the lack of chemotherapy as excuses. In patients with burns of limited extent there is no danger of producing shock and yet early grafting was not tried. Moreover, for many years it has been a common practice, in patients with extensive as well as circumscribed burns, to administer a general anesthetic when scrubbing the wounds before spraying tannic acid. It cannot have been the lack of a nontoxic chemotherapeutic agent because, as pointed out in this paper, penicillin is not even given a chance to play a rôle in the immediate closure of cir-

‡ This statement does not apply to Dr. Donald B. Wells who in 1929 published an article entitled "The Treatment of Electric Burns by Immediate Resection and Skin Graft" in which he described this treatment of three cases.¹² Dr. Wells' treatment resulted from what was learned in the war of 1914-18. He states, "The complete resection of gunshot wounds, more usually spoken of as débridement, and their immediate closure by primary suture or their delayed closure after a few days of chemical sterilization, was a technic developed and perfected during the World War. The application of this principle of complete resection and immediate closure by suture or skin graft to third degree electrical burns has not been reported in the literature, nor has it apparently ever been successfully applied so far as we have been able to learn after diligent inquiry among surgeons who must come into frequent contact with the results of electrical traumata."

cumscribed wounds. Immediate excision and closure precludes infection. It is only in the extensively burned patient, some of whose wounds must await their turn for closure, that a chemotherapeutic agent is needed.

The only explanations at hand for the failure of the surgeon to appreciate the potentialities of early surgical closure of the full-thickness burn wound are his fear of the loss of blood during the excision and the deep rooted fallacy that an unattached graft would survive only on a bed of granulation tissue. The plastic surgeon, who has for years placed free grafts successfully upon the freshly exposed surfaces left after excision of scars, will not be surprised to learn that the base left after excision of burn skin is just as good for the successful take of a graft.

A loss of blood in excising the burn wound is admitted. The volume lost increases with the age and extent of the wound but is never so large that it cannot be replaced. Hemorrhage, therefore, does not exclude surgical excision as a method of getting rid of burn slough. Doctors Connor and Harvey's chemical method of slough separation obviates the blood loss of excision but exchanges for it the loss of time, precious in preventing infection, and an inflammatory base upon which to lay grafts.

SUMMARY

Full-thickness burn wounds of the skin have always presented a challenge to the surgeon. Invariably infected, the patient has languished interminably in the hospital before successful closure has been achieved and, if the wounds were extensive, the patient has suffered from severe malnutrition.

If the challenge is met by prompt surgical excision of the dead tissue and immediate closure of the wound by grafting, infection is precluded, scar tissue with disfigurement and disability are minimized, the period of hospitalization is curtailed, manpower is economized and the outlook of the patient heartened.

The expeditious treatment of 52 full-thickness burn wounds in 38 patients by surgical excision and grafting at the Massachusetts General Hospital is recounted. Circumscribed burns of full-thickness have been excised and closed by grafting within a few hours after injury; the healing is most gratifying. In the wounds where a delay of days between injury and excision was introduced, infection insinuated itself in spite of the administration of systemic chemotherapy and delayed closure was resorted to in half the cases. The results have been surprisingly good. In the patients with extensive full-thickness wounds, homeostasis has been effected and maintained so that areas have been excised and grafted within the first few days. The care of the other areas has had to be postponed because of the precariousness of homeostasis and lack of sufficient donor skin for the grafting. The longer the delay in closure, the greater has been the infection, the less successful the take of the grafts, and the uglier and more disabling the scarring.

It is hard to convince any but the plastic surgeon, with his experience in excising old scars, that the best base upon which to place a graft is the one freshly exposed, even if edematous, after excision of burn slough.

The problem of the recognition of full-thickness destruction resolves itself with experience in practice.

Chemotherapy is a valuable adjunct in holding invasive infection in abeyance in those cases in which the excision and grafting must be delayed and in which the organisms are amenable. Its services are probably superfluous in those patients whose wounds are excised and grafted within the first hours after injury.

REFERENCES

- ¹ Management of the Cocoon Grove Burns at the Massachusetts General Hospital. *ANNALS OF SURGERY*, 117, 801, 1943; and published as a monograph by J. B. Lippincott Company, Phila., 1943.
- ² Manuscript in preparation for publication.
- ³ Connor, Gervase J., and Harvey, Samuel C.: The Pyruvic Acid Method in Deep Clinical Burns. *ANNALS OF SURGERY*, 124, 799, 1946.
- ⁴ Young, Forrest: Immediate Skin Grafting in the Treatment of Burns: A Preliminary Report. *ANNALS OF SURGERY*, 116, 445, 1942.
- ⁵ Ackman, Douglas, Gerrie, John W., Pritchard, J. E., and Mills, E. S.: A Report of the Management of Burns Using the Occlusive Compression Dressing, with Sulfathiazole Emulsion. *ANNALS OF SURGERY*, 119, 161, 1944.
- ⁶ Saltonstall, Henry, and Lee, Walter E.: Modified Technic in Skin Grafting of Extensive Deep Burns. *ANNALS OF SURGERY*, 119, 690, 1944.
- ⁷ McCorkle, H. J., and Silvani, Henry: Selection of the Time for Grafting of Skin to Extensive Defects Resulting from Deep Thermal Burns. *ANNALS OF SURGERY*, 121, 285, 1945.
- ⁸ Berkow, Samuel G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) based on Surface Area Proportions. *Arch. Surg.*, 8, 138, 1924.
- ⁹ Dingwall, James A.: A Clinical Test for Differentiating Second from Third Degree Burns. *ANNALS OF SURGERY*, 118, 427, 1943.
- ¹⁰ Cope, Oliver: The Chemical Aspects of Burn Treatment. *J. A. M. A.*, 125, 536, 1944.
- ¹¹ Rawson, R. W.: The Binding of T-1824 and Structurally Related Diazo Dyes by the Plasma Proteins. *Am. J. Physiol.*, 138, 708, 1943.
- ¹² Wells, Donald B.: The Treatment of Electric Burns by Immediate Resection and Skin Graft. *ANNALS OF SURGERY*, 90, 1069, 1929.

ESOPHAGEAL ATRESIA AND TRACHEO-ESOPHAGEAL FISTULA

WILLIAM E. LADD, M.D.,* AND ORVAR SWENSON, M.D.†

BOSTON, MASS.

FROM THE DEPARTMENT OF SURGERY, HARVARD MEDICAL SCHOOL, AND SURGICAL SERVICE,
THE CHILDREN'S HOSPITAL, BOSTON, MASS.

ESOPHAGEAL ATRESIA and tracheo-esophageal fistula received comparatively little recognition or interest from clinicians until the last decade, or so, in spite of the fact that the condition had been described by Durston,¹ in 1670, by Gibson,² in 1703, and by Martin,³ in 1821. It is now realized that the anomaly is quite common. Sir G. Gray Turner⁴ has recently estimated that the malformation occurs about as frequently as hare lip and cleft palate. It is undoubtedly true that many infants still die of esophageal atresia without its having been diagnosed.

EMBRYOLOGY

It should be recalled that the esophagus and trachea in early fetal life are one tube. Between the fourth and twelfth week of fetal life this tube becomes divided into two by an ingrowth of mesoderm. During this same period the lumen of the esophagus becomes obliterated by the rapid proliferation and concrescence of its epithelial lining. Later, this solid cord becomes vacuolated, the vacuoles coalesce, and the lumen is reestablished in the same manner as in the intestine. An arrest in development, or failure of the mesoderm completely to separate the trachea from the esophagus, results in the tracheo-esophageal fistula, while failure of the vacuoles to coalesce results in the atresia of the esophagus.

PATHOLOGY

There is a wide variation in the pathologic findings of these anomalies; in fact, it may be said that no two cases are exactly alike. However, they may be roughly divided into five types, as shown in the diagram (Fig. 1) previously published by Ladd,⁵ and described as follows:

"In Type I, the upper portion of the esophagus ends in a blind pouch in the region of the body of the first or second dorsal vertebra, and the lower segment of the esophagus begins again in a blind pouch at the level of the fourth or fifth dorsal vertebra. In Type II, the upper segment of the esophagus ends in a fistulous tract entering the trachea just above its bifurcation, whereas the lower segment is much the same as in Type I. In Type III, the upper segment ends blindly as in Type I, whereas the lower segment is connected to the trachea just above its bifurcation by a fistulous tract. This type and Type

* William E. Ladd, Professor of Child Surgery, Emeritus, Harvard Medical School, and Surgeon-in-Chief, Emeritus, The Children's Hospital, Boston, Mass.

† Associate Surgeon, The Children's Hospital, Junior Associate in Surgery, Peter Bent Brigham Hospital, and Instructor in Surgery, Harvard Medical School, Boston, Mass.

IV are by far the most common in the reports of the literature as well as in our own experience. Type IV is similar to Type III except that the fistulous tract of the lower segment enters the trachea at its carina instead of just above its bifurcation. In Type V, both the upper and lower segments communicate with the trachea, as shown in the diagram."

CLINICAL FINDINGS

If a newborn infant becomes cyanotic and shows an excess of saliva or frothy mucus in the mouth, the diagnosis of esophageal atresia should be considered. If subsequently the infant vomits all fluid offered, almost immediately

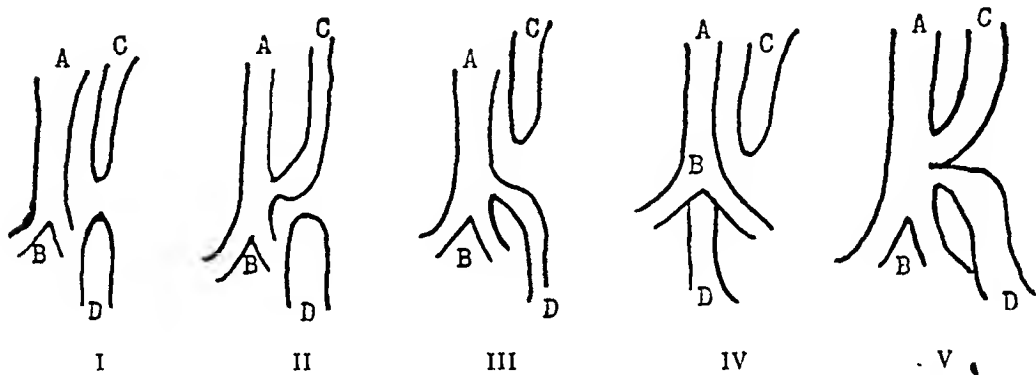


FIG 1.—Diagram showing the arrangement of the trachea and esophagus in the various types of esophageal atresia and tracheo-esophageal fistula.

The letters refer to the following structures: A—trachea; B—bifurcation of trachea; C—upper segment of esophagus; and D—lower segment of esophagus. (From *New England Journal of Medicine*, 230:625-637, May 25, 1944.)

after it is given, the diagnosis should be strongly suspected and steps taken to confirm or disprove the suspicion. First, a No. 8-F. or 10-F. soft rubber catheter should be introduced into the esophagus, preferably under the fluoroscope, and if this meets obstruction 10 or 12 cm. from the lips, the diagnosis is confirmed.

ROENTGENOLOGIC EXAMINATION

The diagnosis should now be refined to differentiate between the types of the malformation. This may be done with the help of the roentgen ray. With the soft rubber catheter at the point of obstruction, not more than 0.5 cc. of lipiodol is inserted and watched under the fluoroscope, to determine whether there is any connection between the upper segment of the esophagus and the trachea. If a large amount of lipiodol is introduced into an esophagus that ends blindly, it will be regurgitated and aspirated into the trachea and lungs, and confuse the picture. Of course, this same thing would happen if barium were given, which makes its use contraindicated.

Subsequent to the fluoroscopic examination, a roentgenogram should be

taken of the chest and abdomen. The chest film will demonstrate the level of the blind end of the upper segment of the esophagus, which is an important factor in determining the plan of operation. It will also supplement the physical examination in estimating the amount of atelectasis or pneumonia, which is usually present in these patients. The examination of the abdomen roentgenologically will show the presence or absence of air in the stomach and intestines.

If the patient has a Type I or II malformation, there obviously will be no air in the stomach or intestines (Fig. 2).

Type II may be recognized by the lipiodol entering the trachea from the esophagus, and showing no air in the stomach.

Types III and IV will show air in the stomach and intestines and no lipiodol entering the trachea from the esophagus (Fig. 3).

Type V, of course, will show air in the stomach and intestines but will also show lipiodol entering the trachea from the esophagus.

Roentgenologic examination of the patient will help the surgeon to determine the preferable plan of treatment, but it should be remembered that associated anomalies may be present and should be sought for before the operation is begun.

The associated anomalies, though frequent, are only rarely of importance in the life or health of the child. Table I represents all the anomalies that have been noted in 114 cases. Although these add up to 91 malformations, in some instances more than one anomaly occurred in one patient, and many were not of a serious nature.

In Table II are classified the number of serious malformations which were observed in the 82 patients who have been admitted to The Children's Hospital since 1939 with esophageal atresia. It is estimated that 18 of these malformations either made it necessary to modify the treatment, or caused the death of the baby.



FIG. 2.—Roentgenogram.

PREOPERATIVE PREPARATION

The preoperative preparation of these patients is important. They almost always have respiratory difficulties (pneumonia, or atelectasis) due to aspiration of saliva and mucus. The infant should be placed in an oxygen tent for the administration of oxygen in high concentration. Then a small soft rubber

catheter is introduced into the pharynx and attached to constant suction. By this means, and keeping the infant in a slight Trendelenberg position, the air passage can be kept fairly clear and respiration made much easier. A small transfusion and parenteral fluids should be given as indicated, care being taken not to overtax the circulation and cause pulmonary edema. Such preoperative preparation will often improve the patient's condition sufficiently to make an operation successful which otherwise would certainly end in disaster.

TABLE I

ANOMALIES ASSOCIATED WITH ATRESIA OF THE ESOPHAGUS

Type	No. of Cases
Atresia or stenosis of the small intestine.....	7
Meckel's diverticulum.....	8
Malrotation.....	4
Imperforate anus.....	11
Fistula of the rectum.....	4
Anomalies of the heart and aorta.....	20
Congenital anomalies of the urinary system.....	13
Miscellaneous.....	24

TABLE II

SERIOUS ANOMALIES IN THE LAST EIGHTY-TWO CASES

Type	No. of Cases
Atresia or stenosis of intestine.....	5
Imperforate anus.....	5
Congenital heart.....	13
Anomalies of the urinary tract.....	2

OPERATIVE APPROACH

All attempts to remedy esophageal atresia with tracheo-esophageal fistula, without direct ligation of the fistula, have failed.

The direct approach to the site of the atresia and fistula may be made through the left back or the right back, and may be transpleural or retropleural. In 1941, Mr. R. H. Franklin⁴ performed a primary anastomosis through a transpleural approach, but the patient unfortunately died 17 hours later. At the Children's Hospital this transpleural approach has been used on seven patients. Doctor Swenson used this approach to tie off the tracheal fistula (See Case Report No. 304556) in one patient with other malformations, and the baby survived. Doctor Gross used it on five patients with one successful primary anastomosis and four fatalities, and Doctor Ladd used it once without success.

This transpleural approach has some theoretic advantages. With the long intercostal incision or a resection of a long segment of the fifth rib an excellent

exposure may be obtained quickly with slight injury to the thoracic cage. However, while this approach is made more quickly, the closure is time-consuming and the total operating time is not diminished. Furthermore, if a leak takes place at the anastomosis the chest fills with saliva and gastric contents, and in all cases in which this complication has occurred the outcome has been fatal. If the retropleural approach is used and a similar complication arises, a fistula to the back is established, and in several such instances the baby has survived. We, therefore, prefer the retropleural approach through the right back.

Although Dr. Cameron Haight⁶ has reported successful results using the route through the left back, in the two instances in which we have used that approach the result has been fatal. All but two of our favorable results, and the majority of those found in the literature, have been accomplished by retropleural operations through the right back.

TECHNIC OF OPERATION

Cyclopropane has been the anesthesia of choice in our experience. If local anesthesia is used it should be supplemented by a closed system with oxygen to combat collapse of the lung in case the pleura is inadvertently opened. An intravenous needle is inserted into an ankle vein for the administration of blood or fluid during the operation. The patient is placed on the operating table left side down, with a folded towel to give the spine a slight curve with the convexity upward toward the right side. The right arm is abducted to displace the scapula laterally.

An incision is now started at the level of the second rib between the internal border of the scapula and the spine. This incision is carried downward to the level of the sixth rib where it swings laterally for two or three centimeters. After the incision has been carried through the trapezius and rhomboid muscles the scapula is displaced laterally and the ribs exposed. In our earlier cases a rather long section of the fourth rib was resected and short sections of the third and fifth were resected or only cut. More recently, however, a better exposure has been obtained by resecting one to two centimeters of the second to the fifth ribs, inclusive, or the third to the sixth, according to the level of the upper blind pouch of the esophagus. This approach more closely resembles that recommended by Haight.⁶

After the small sections of rib have been resected, the intercostal muscles, with the intercostal vessels and nerves, are tied and cut. The pleura is then carefully freed from the posterior thoracic wall, toward the bodies of the vertebrae. The first anatomic landmark is the sympathetic chain, with its

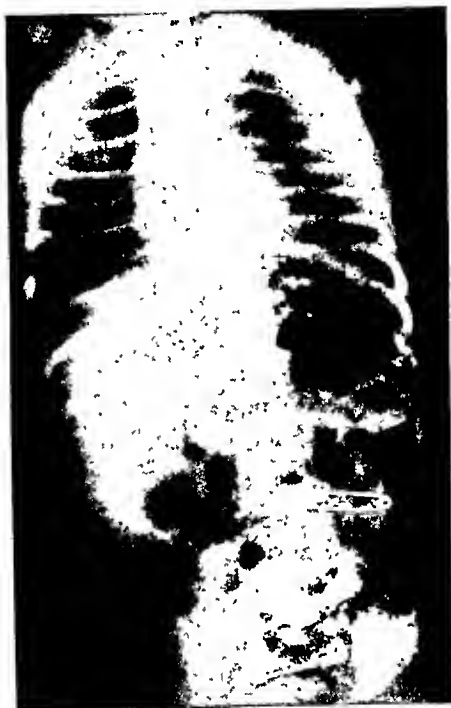


FIG. 3.—Roentgenogram.

ganglia. The azygos vein then comes into view, and this is isolated until its terminal trunk is exposed as it crosses the mediastinum. This is then tied and cut. When the two ends are pushed aside, the vagus nerve is readily located and this gives a direct lead to the segments of the esophagus.

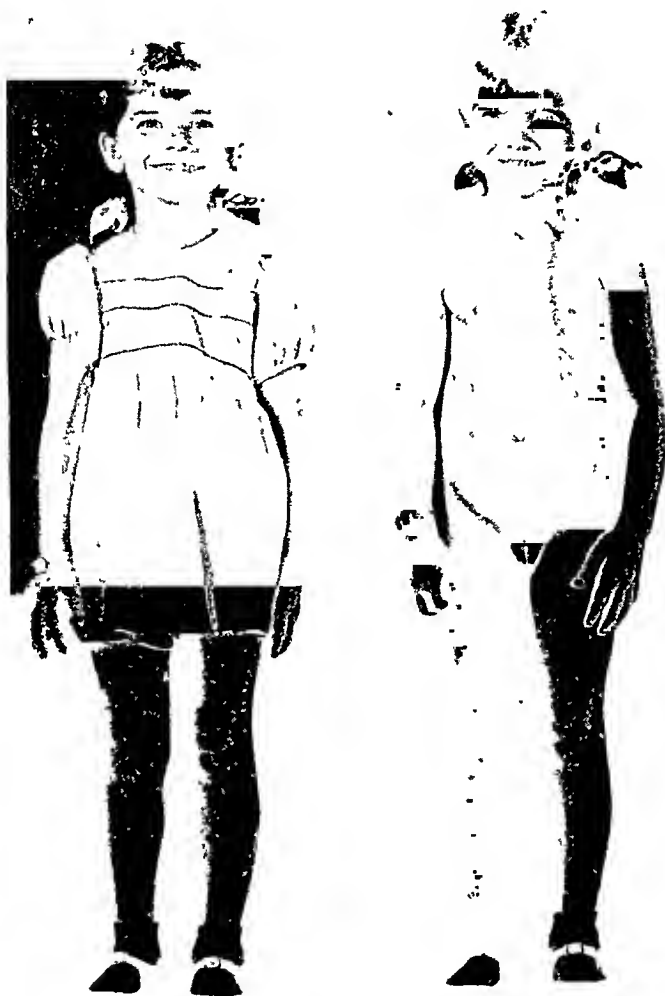


FIG. 4.—This is Doctor Ladd's oldest patient, now six and one-half years of age. She takes a normal diet by mouth, attends school, and engages in all activities of a normal child.

It is at this point that judgment and experience are of value in determining whether to attempt a primary anastomosis, or to perform the simpler operation of tying and cutting the tracheo-esophageal fistula. This decision depends on two factors. the condition of the patient, and the distance between the two ends of the esophagus. If the space between the two segments of the esophagus is much over two centimeters, the possibility of being able to do an anastomosis without tension is not good.

ATRESIA AND FISTULA OF ESOPHAGUS

PRIMARY ANASTOMOSIS

When the conditions indicate the desirability of an end-to-end anastomosis, the following steps are taken: First, the upper, blind end is freed well up above the first rib, so that it can be brought to the lower end without tension. Next,



FIG. 5.—A. A rope graft has been made on the right lateral aspect of the chest and right axilla.

B. Three weeks later the lower end of the rope was swung and sutured to a point just above the esophagostomy.

C. The dermic tube has been turned in and covered with the rope graft. The patient is now ready to have a jejunal segment anastomosed to the skin tube.

the lower segment is isolated and is cut away from the trachea almost in the tracheal wall, in order to give it maximum length. As the esophagus is separated from the trachea, the opening into the trachea is closed by a running

suture of fine silk, and this row of sutures is, in turn, covered by a second layer of running sutures of the same material. The final step is the suturing together of the two ends.

In our recent cases, the musculature is first approximated on the back of the esophagus by interrupted fine silk stitches, including muscle layer only.

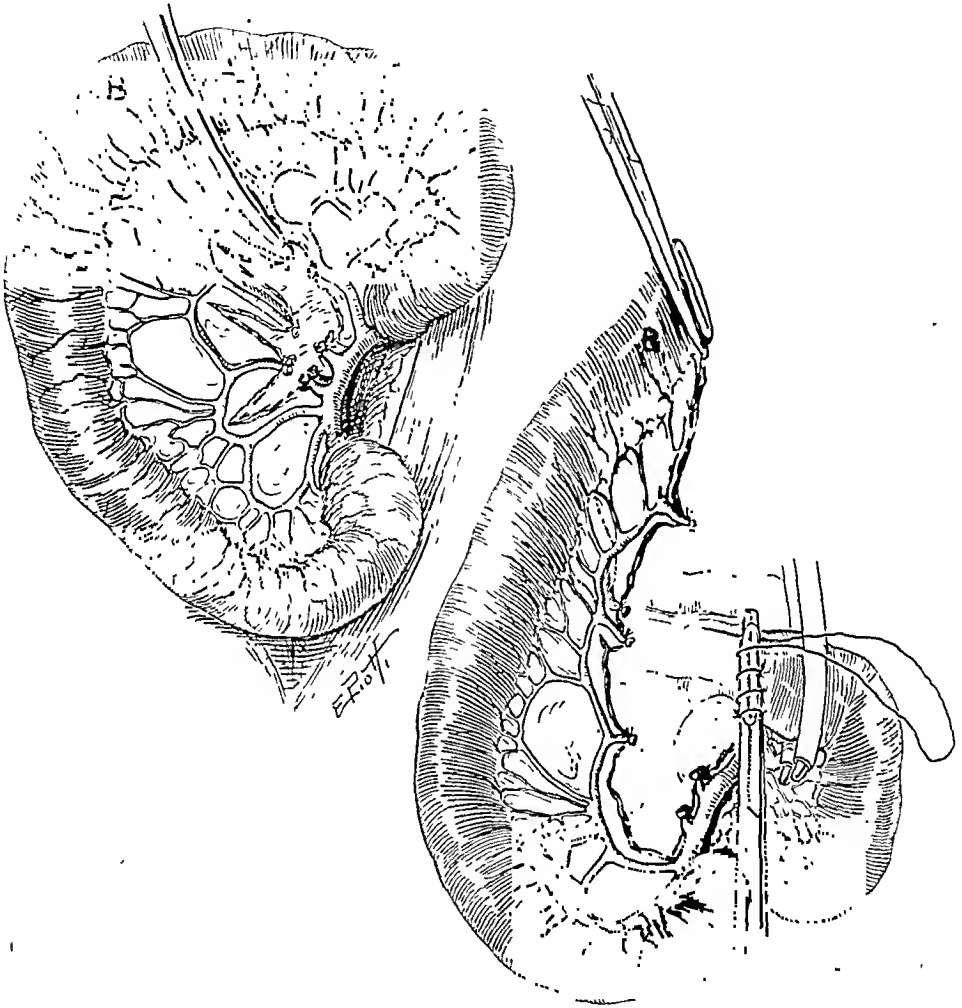


FIG. 6.—Note in drawing two intestinal vessels have been cut and the mesentery has been divided up to the first arcade, thus freeing a segment of jejunum.

Approximation stitches are then placed in the mucous membrane, likewise on the back part of the esophagus. The interrupted sutures are then applied to the front part of the esophagus to complete the closure of the mucous membrane, and following this a second layer of interrupted stitches is applied to the musculature only.

After the anastomosis has been completed, about 10 cc. of penicillin, containing 5,000 units per cc., is placed in the retropleural space, and a small rubber dam drain is inserted to the mediastinum. The opening in the chest

wall is closed to the drain by suturing together, first the intercostal bundles, then the rhomboids, and then the trapezius. Finally, the skin is closed over this with an interrupted or a running silk suture.

In our first successful cases of direct anastomosis, the catheter which was in the upper blind pouch during the operation was introduced into the stomach through the anastomosis and left in place for a week or ten days. More recently, the catheter, which it is desirable to have in the upper segment of the esophagus during the operation, has been removed at the end of the operation. We feel that this diminishes the chance of respiratory infection and of infection of the anastomosis. Postoperatively, the patient's fluid balance is maintained by transfusion of blood or plasma, and by intravenous fluids of saline or glucose. During this period, also, the patient is kept in an oxygen tent. In from 24 to 48 hours, according to the condition of the patient, gastrostomy is performed for feeding. In case there is no leakage from the anastomosis, feedings by mouth are begun at the end of the 10th to 12th day. In case of leakage, feeding by mouth is postponed until the fistula has closed.

MULTIPLE-STAGE

In patients in whom the ends are too widely separated to warrant a primary anastomosis, a multiple-stage procedure is adopted. At the first operation the site of the atresia is approached exactly as described for the operation of primary anastomosis. The lower segment of the esophagus is cut away from the trachea at the site of the fistula, both ends tied, and an over-and-over stitch placed to insure against leakage. This having been done, the chest wall is closed as before.

During the next few days the patient is kept in slight Trendelenberg position and constant suction applied to the upper segment of the esophagus to prevent aspiration of saliva and mucus. In this interim the baby's fluid balance is maintained by intravenous administration of blood or plasma, and saline or glucose solutions. At the end of two or three days, under local or cyclopropane anesthesia, a gastrostomy is performed through a high left rectus incision. This enables the infant to be fed and obviates the necessity of continuing parenteral fluids.

The third stage of the operation is performed one or two days after the gastrostomy, and consists of bringing the upper segment of the esophagus out in the neck. The procedure is to make a small inverted V-shaped incision 1.5 cm. above the clavicle, starting at the midline and carrying it laterally to the left for a distance of 3.5 cm. The trachea is displaced from the operative field by extending and rotating the head to the right. The fibrous band extending downward from the lower end of the upper segment of the esophagus into the mediastinum must be cut before the blind end can be delivered. The esophageal pouch is opened and the cut edges approximated to the skin with interrupted silk sutures. Now the patient can swallow saliva and is no longer in danger of aspiration pneumonia.

After these procedures have been completed, an indefinite period may elapse before the anterior thoracic esophagus is constructed.

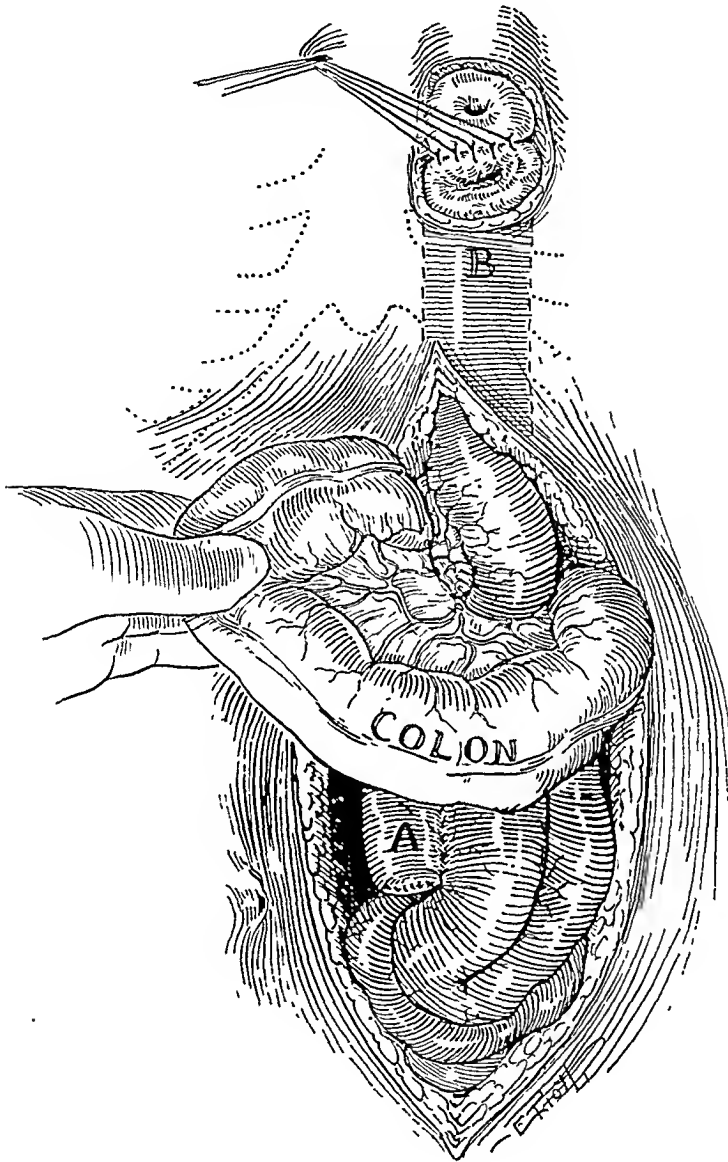


FIG. 7.—The freed segment of jejunum has been tunneled under the skin of the lower chest wall. The jejunum is being anastomosed to the skin tube. A side-to-side anastomosis has been made between the proximal and distal segments of the jejunum.

ANTERIOR THORACIC ESOPHAGUS

Surgeons have employed many methods of constructing an anterior thoracic esophagus. In our oldest patient, now over six and one-half years old, the stomach and esophagus were connected by an epithelial-lined tube made over the left chest wall and covered by a tube graft taken from the right axilla. The

ATRESIA AND FISTULA OF ESOPHAGUS

child upon whom this series of operations were performed is a happy and healthy girl, who takes a varied diet by mouth, goes to school, and leads a nearly normal life. Occasional dilatations of the anastomosis between the skin tube and the stomach are necessary. The details of this method were described in a previous communication⁵ (Fig. 4).



FIG. 8

FIG. 8.—A photograph of patient No. 267162, now four years of age. It is more than a year since completion of the anterior thoracic esophagus. A regular diet is taken without difficulty.



FIG. 9

FIG. 9.—Note the catheter in the upper blind pouch, markedly dilated heart, and tremendous distention of stomach and duodenum, with no air in the intestinal tract below the duodenum.

Although anastomosis of the skin tube directly to the stomach has been successful in one case, there are obvious disadvantages. These may be obviated by uniting the skin tube to a jejunal segment. The steps in this operation are as follows: First, a tube or rope graft is elevated in the right axilla and the raw surface underlying this covered by a Thiersch graft. At the end of three weeks the lower end of this tube graft is freed, swung up to the left side of neck and implanted just above the esophagostomy. After approximately another three weeks, when it has acquired adequate circulation, the new esophagus is ready to be constructed. This is done by turning down a V-shaped flap from above the esophagostomy and under the attachment of the tube graft. Next, two parallel incisions are carried downward on the left chest wall. These

release the skin flaps which are turned toward each other and sutured together and to the V-shaped flap of skin which has been turned downward from the neck. Thus, is formed an epithelial-lined skin tube leaving a raw surface outside. The axillary end of the tube graft is now detached, the tube is unfolded and used to cover the raw surface left by making the skin-lined esophagus (Fig. 5).

After these wounds are completely healed, and any induration which may be present has subsided, the next step is to unite a segment of jejunum to this skin tube. This is done through a left rectus muscle-splitting incision extending downward from the costal margin. The proximal loop of jejunum is iden-



FIG 10.—Case No. 306150: Fifteen days postoperatively. At this time all feedings were well taken by mouth.

tified and one of the first intestinal vessels is isolated, ligated, and divided as close to the mesenteric artery as possible. The jejunum is divided about six inches from the ligament of Treitz and the mesentery divided from this point on the bowel to the divided mesenteric vessel. Closure of the proximal end of the jejunum is now carried out. The distal segment is free and is usually long enough to extend 6 or 8 cm. on the chest wall above the costal margin. Should the distal segment fail to reach such a position, the mesentery can be freed further by division of a second intestinal artery and vein close to the mesenteric vessels. The avascular portion of the mesentery up to the first arcade is divided, giving sufficient length to the distal segment of jejunum (Fig. 6). The skin of the chest is tunneled under from the cephalic end of the incision to a point under the opening of the skin tube.

An incision is made across the bottom of the skin tube and the overlying skin is separated from the dermic tube. Anastomosis of the skin tube is accomplished by a posterior row of interrupted fine chromic catgut sutures through the serosa and muscular coats of the jejunum to the subcutaneous tissue of the skin tube. A row of chromic catgut sutures is placed through all layers of the jejunum and the skin of the tube. The anastomosis is completed anteriorly by a row of interrupted chromic catgut sutures through the serosa and muscular coats of the jejunum and the subcutaneous tissue (Fig. 7).

ATRESIA AND FISTULA OF ESOPHAGUS

This procedure is a combination of parts of technic previously published by Wullstein,⁷ Davis,⁸ and Ladd.⁵

Providing there is no evidence of inflammation at the site of the dermo-jejunal anastomosis, the patient is given water by mouth on about the tenth postoperative day. In two out of five cases fistulae developed at this point, but both closed spontaneously.



FIG. 11.—This child is now eight months postoperative, and doing well. She is a perfectly normal child, taking a regular baby diet. Dilatations of the esophagus have not been necessary.

The ease with which these patients can swallow liquids and solids is gratifying. Only occasionally is it necessary to promote the emptying of the skin tube by manual pressure.

SUMMARY OF TWO UNUSUAL AND FOUR TYPICAL CASES

Case No. 267162.—Surgeon W. E. L.: This patient was first admitted October 19, 1942, and a diagnosis of esophageal atresia and tracheo-esophageal fistula was made. Exploration of the mediastinum was carried out with ligation of the fistula. Two days following this, gastrostomy and marsupialization of the esophagus were performed. He

did well until the sixteenth postoperative day, when he coughed up some material resembling formula. Reexploration of the mediastinum demonstrated the reestablishment of the tracheo-esophageal fistula. This was ligated and divided.

At 15 months of age an anterior dermo-esophagoplasty was performed in three stages. At the age of two years and seven months a jejunal segment was brought up and anastomosed to the skin tube. On the tenth postoperative day liquids were taken well by mouth and the patient was soon able to take solids. It is only occasionally necessary to manually decompress the skin tube. At the age of four years he continues to do well but has had one dilatation of the skin-tube-jejunal anastomosis, which was probably unnecessary (Fig. 8).

Case No. 286815.—Surgeon W. E. L.: This infant had esophageal atresia of Type III and an associated duodenal atresia and congenital heart disease. At the first operation



FIG. 12.—This is patient No. 298835 at six months of age, after primary anastomosis of the esophagus. He has no difficulty in taking a normal baby diet. Dilatations of the esophagus have not been necessary.

the tracheo-esophageal fistula was excised and a duodenojejunosomy and gastrostomy performed. A few days later the upper blind segment of the esophagus was marsupialized in the neck. The patient is now two years old, in excellent health, and awaiting the construction of an anterior thoracic esophagus.

Case No. 306150.—Surgeon W. E. L.: This four-day-old baby was admitted with a diagnosis of atresia of the esophagus with tracheo-esophageal fistula. After 24 hours of preparation the mediastinum was explored through a right-sided retropleural approach. A Type III fistula was found, which was ligated and divided. The upper esophageal pouch was about 0.5 cm. above the fistula and when freed could be brought down to the lower segment with little if any tension.

A primary anastomosis was made and postoperatively the baby did well. On the first postoperative day a gastrostomy was carried out under local anesthesia. Feedings by gastrostomy were well tolerated, and on the tenth postoperative day feeding by mouth in small amounts was started. By the 15th day after operation all feedings were taken orally, and the patient had gained in weight by the 16th day. The gastrostomy tube was removed. The baby was discharged on the 18th postoperative day (Fig. 10).

Case No. 297981.—Surgeon O. S.: This four-day-old baby girl was unable to take and retain even small amounts of fluid. Soon after the diagnosis of atresia of the esophagus with tracheo-esophageal fistula was made, and verified roentgenologically, the mediastinum was explored and a Type III tracheo-esophageal fistula was found. The upper esophageal

pouch was on the same level with the tracheo-esophageal fistula, so that a primary anastomosis could be made without tension on the suture line.

Postoperatively, the baby did well, in spite of evidence of congenital heart disease. Gastrostomy was performed under local anesthesia on the second postoperative day. Feedings by gastrostomy were well tolerated, and on the 10th day feedings were gradually started by mouth. By the 12th day all feedings were taken by mouth and the child was discharged home on the 19th postoperative day, where she has continued to do well, gain weight, and take her feedings without difficulty (Fig. 11).

Case No. 298835.—Surgeon O. S.: This four-pound, four-ounce baby boy was admitted to the Children's Hospital at two days of age, with the diagnosis of esophageal atresia and tracheo-esophageal fistula. A mediastinal exploration was performed through a right retropleural approach. A Type III fistula was found and divided. As the two esophageal segments were only one centimeter apart, a primary anastomosis was made.

Postoperatively, the child did well, and on the second day gastrostomy was performed under local anesthesia. He developed bilateral bronchopneumonia and was severely ill for several days. On the 10th day feedings in small amounts were given by mouth. He was discharged on the 30th postoperative day, and has continued to do well at home. He is now eight months old. (Fig. 12).

Case No. 304550.—Surgeon O. S.: This two-day-old baby was admitted with a diagnosis of esophageal atresia and tracheo-esophageal fistula. The abdomen was markedly distended and a roentgenogram demonstrated atresia of the terminal ileum. Bile-stained material was coughed up by the baby.

Through a transthoracic approach the tracheo-esophageal fistula was ligated and divided. Although the upper esophageal segment was within 1.5 cm. of the fistula a primary anastomosis was not done, as the time consumed would have been prohibitive. A long abdominal incision was made, and a malrotation and atresia of the ileum with a minute cecum and colon were found. The terminal ileum ended in a bulbous sac about five centimeters in diameter. The malrotation was corrected and the terminal bulbous ileum was resected with a Mikulicz spur between the terminal ileum and cecum. A gastrostomy was also made. Nineteen days later the ileostomy was closed. Two weeks later a primary anastomosis of the esophagus was made through a retropleural approach. Ten days later feedings were well taken by mouth. The patient continued to do well, and was discharged taking all feedings by mouth and gaining weight (Fig. 13).



FIG. 13.—Roentgenogram of patient No. 304556. This upright film shows consolidation consistent with pneumonia or atelectasis, and evidence of atresia of the lower ileum.

RESULTS

Since January, 1939, 82 cases of esophageal atresia have been seen at the Children's Hospital. Of this number, 76 have been operated upon by Ladd.

Gross, and Swenson. Four of the remaining six cases were moribund at the time of admission to the hospital, dying within a few hours. Two with multiple associated anomalies, operated upon by other members of the staff, will not be included in the consideration of the results. Table III shows the results obtained in this series of 76 cases.

TABLE III

SUMMARY OF CASES OF ATRESIA OF THE ESOPHAGUS
WITH TRACHEOESOPHAGEAL FISTULA
AT
THE CHILDREN'S HOSPITAL
JANUARY 1940-JULY 1946

SURGEON	NUMBER OF CASES MULTIPLE STAGE OPERATION		NUMBER OF CASES PRIMARY ANASTOMOSIS		TOTAL NUMBER OPERATIONS		MORTALITY	REMARKS
	LIVING	DEAD	LIVING	DEAD	LIVING	DEAD		
LADD	15	21	4	7	19	28	59%	ONE DEATH RESULTED FROM PERITONITIS AFTER THE COMPLETION OF AN UNSATISFACTORY ANTERIOR THORACIC ESOPHAGUS. ONE DEATH WAS OF UNKNOWN CAUSE FOLLOWING IMMUNIZATION FOR MEASLES, ALSO AFTER THE COMPLETION OF ANTERIOR THORACIC ESOPHAGUS.
GROSS	0	3	4	10	4	14	76%	THREE DEATHS OCCURRED IN PRIMARY ANASTOMOSIS CASES BY THE TRANS-PLEURAL ROUTE. ONE HAD OTHER SERIOUS MALFORMATIONS. ONE PATIENT WHO HAD DUODENAL STENOSIS HAD AN ABDOMINAL OPERATION ONLY DIED AND IS NOT INCLUDED IN THE TOTAL CASES.
SWENSON	1	3	6	1	7	4	36%	ONE SURVIVING PATIENT HAD AN ILEAL ATRESIA AND FIRST THE TRACHEAL FISTULA WAS TIED OFF BY THE TRANSPLEURAL ROUTE AND LATER A PRIMARY ANASTOMOSIS BY THE EXTRAPLEURAL APPROACH WAS CARRIED OUT.
TOTAL	16	27	14	18	30	45	60%	

COMMENTS

The time has obviously passed when obstetrician, or pediatrician, should advise parents of infants with esophageal atresia that nothing can be done for them. The time has now come when alertness in making an early diagnosis of this disease may lead to successful treatment. Obstetricians and pediatricians have the opportunity of seeing these patients first, and mortality in the future will depend to a large extent on their quick recognition of the condition and prompt transfer of the patient to a hospital equipped to care for the child properly.

The operation of primary anastomosis, done *via* an approach through the right back, is beyond question the operation of choice when feasible. Our recent results strongly suggest that the suturing should be done with two rows

of interrupted fine silk sutures, one to the mucous membrane and one to the musculature. This belief agrees with the experimental work done by Swenson and Magruder⁹ in suturing the esophagus in animals. To avoid strain on the suture line, it may be supplemented by the whip-stitch previously described by Ladd⁵ or perhaps better by fixing the upper segment of the esophagus to the fascia of the chest wall (as practiced by Swenson). The use of penicillin locally in the mediastinum, followed by the administration of penicillin and sulfadiazine, as well as elimination of the catheter through the anastomosis, have probably been factors in reducing the mortality due to infection. Our last seven cases of primary anastomosis record no deaths.*

The multiple-stage operation should be employed only in those patients in whom the two ends of the esophageal segments are so far apart that they can not be sewed together without tension, or in those patients who have serious associated anomalies, or who for some other reason are particularly bad risks. The multiple-stage procedure requires prolonged hospitalization and much patience on the part of the surgeon. However, as a method of the immediate avoidance of a fatality, it has its place. We have now five cases in which the anterior thoracic esophagus has been completed. It is functioning satisfactorily in four of them, and we feel should function well in the fifth but for the child's being mentally deficient. We have 11 other patients awaiting the construction of an anterior thoracic esophagus.

The senior writer feels that in the early part of the series he made mistakes in both directions in the selection of plan of operative treatment. That is, he has attempted primary anastomosis in some cases where the multiple-stage procedure was indicated in view of present knowledge, and *vice versa*. In the latter part of the series, both writers have profited by early mistakes. As the result of our experience, the mortality from esophageal atresia should be still



FIG. 14.—This three-year-old child is the oldest living patient of Doctor Ladd, with a primary anastomosis, in our series. She is a perfectly normal child, taking a regular diet. Dilatations were performed during the first year. They have not been necessary during the past two years.

* Since submitting this communication for publication, there have been an additional seven cases, with one death.

further reduced. There undoubtedly will continue to be an appreciable mortality due to associated anomalies incompatible with life.

REFERENCES

- ¹ Mackenzie, M.: A Manual of Diseases of the Throat and Nose. William Wood & Co., New York. 2, 149-158, 1884.
- ² Gibson, T.: Anatomy of Human Bodies Epitomized. London, p. 240.
- ³ Martin: Exposé des travaux de la Soc. roy. de méd. de Marseille. Marseille: Kreuter, Legrand, Weber, 1821. p. 44.
- ⁴ Turner, Sir G. Gray: The Newcastle Medical Journal. Vol. XXII. January, 1944 and 1945.
- ⁵ Ladd, William T.: The Surgical Treatment of Esophageal Atresia and Tracheo-esophageal Fistulas. N. E. Jour. of Med. 230, 625-637, May 25, 1944.
- ⁶ Haight, Cameron: Congenital Atresia of the Esophagus with Tracheo-esophageal Fistula. ANNALS OF SURGERY, 120, 623-651, 1944.
- ⁷ Wullstein, L.: Über antethorakale Oesophago-jejunostomie und Operationen nach gleichen Prinzip. Deutsche med. Wchnschr., 30, 734, 1904.
- ⁸ Davis, J. Staige, and Stafford, E. S.: Successful Construction of an Anterior Thoracic Esophagus. J. Hopkins Hosp. Bull., 71, 191-212, 1942.
- ⁹ Swenson, Orvar, and Magruder, Thomas V. Jr.: Experimental Esophagectomy. Surgery 15, 954-963, 1944.

PULSION DIVERTICULUM OF THE PHARYNGO-ESOPHAGEAL JUNCTION: TECHNIC OF THE ONE-STAGE OPERATION*

A PRELIMINARY REPORT

RICHARD H. SWEET, M.D.

BOSTON, MASSACHUSETTS

FOR MANY YEARS there has been a division of opinion among surgeons concerning the technic to be used in the operation for excision of diverticula of the pharyngo-esophageal junction. Early attempts to perform the operation in one stage led to discouragement as a result of the frequent occurrence of deep cervical or mediastinal infection and the development of fistulae. To avoid these complications it seemed logical to divide the operation into two stages: The first, including merely the mobilization of the diverticulum and its implantation in the superior portion of the wound; and the second, involving the actual excision of the sac and the closure of the opening at its neck. The late Dr. Charles Mayo^{1, 2} was an early advocate of this method. More recently, Lahey has done much to popularize the two-stage technic.³

A review of the technical details of the earlier one-stage methods suggests the reasons for the difficulties which were encountered. Large sizes of ligatures and suture material (often chromic catgut) were frequently used. The diverticulum was usually tied at its neck, cut with the cautery or with a knife moistened with carbolic acid, and its stump inverted with a purse-string suture into the wall of the esophagus. An abscess resulting from the necrosis of this ligatured stump would then form in the wall of the esophagus or hypopharynx. If this broke into the lumen as a result of the cutting through of the ligature, no serious immediate consequence was experienced, although the delayed healing eventuating from this tended to result in a stenosis in some cases. In these, subsequent dilatation was necessary. If the abscess around the necrotic stump broke through the outer wall, the inevitable infection, followed by fistula formation, was often of serious consequence. The development of infection and fistulae was often further forwarded by the use of an inlying stomach tube or by instrumentation with a bougie or an esophagoscope at the time of performing the operation in an attempt to make it easier to find the diverticulum. In some cases also the tendency toward the occurrence of infection was possibly increased by the injudicious use of drains.

Although the two-stage operation has been shown to minimize to a large extent the occurrence of serious infection such as acute postoperative mediastinitis, it has not prevented the occasional development of a fistula. It is subject also to the objection which can be used against all two-stage surgical procedures, that in addition to the increased annoyance to the patient, it prolongs to a very appreciable extent the duration of stay in the hospital. Harrington,⁴ in a recent review, in which he states that he has given up the two-stage operation, points out that the duration of hospitalization averages more

* From the Surgical Services of the Massachusetts General Hospital.

than two weeks longer with the two-stage procedure than when the one-stage operation is used.

TECHNICAL PRINCIPLES

The adoption of certain elementary details of technic and the utilization of the protection against infection which may be provided by chemotherapeutic agents, such as penicillin and sulfadiazine, make it possible to abandon the two-stage operation in favor of a one-stage procedure which can be expected to result in a minimum of complications and which greatly shortens the period of hospitalization during the recovery period.

No organ of the body responds more kindly to careful handling than the esophagus. It is a thin-walled, delicate structure which lacks a serosal covering. Its blood supply is segmental in origin. In handling it, unnecessary trauma must be avoided. Forceps should be delicate and used sparingly. Allis or Babcock clamps should never be applied to its walls. Dissection must be accurate and no more extensive than necessary, in order to avoid damage to the blood vessels. Sutures must be placed with care and tied without tension so as to avoid crushing the tissues. The layers must be approximated accurately. Cut-edges should never be seared with a cautery, crushed with a clamp, or treated with caustic liquids, such as carbolic acid. In short, any suture of the wall of the esophagus, whether in the performance of an anastomosis or the closure of the opening left after excising a diverticulum, must (1) avoid damage to the cut-edge; (2) secure an accurate layer-by-layer approximation of the edges to be united; and (3) insure an adequate blood supply to the sutured edges.

The adoption of these principles of technic is of primary importance. But there can be little doubt that the additional assistance to be obtained by using sulfadiazine and penicillin to increase the resistance to infection is also important to obtain the best results.

The chances of success are further increased by avoiding all extraneous sources of trauma to the newly sutured edges, such as inlying tubes within the lumen of the esophagus and drains placed too close to the suture line. The use of a drain is not necessary if the field is absolutely dry at the conclusion of the operation.

PREOPERATIVE PREPARATION

The patient should be in the hospital a few days before the performance of the operation to provide an opportunity for thorough evaluation of his general physical condition. This preliminary period, furthermore, allows the patient to rest and to become adjusted to the hospital routine. During the 48 hours immediately preceding operation five grams of sulfadiazine is given each day and 12,000 units of penicillin are administered intramuscularly every three hours.

TECHNIC OF OPERATION

The operation is performed under ether anesthesia, using an intratracheal tube. The left side of the neck is chosen unless the case happens to be one

PHARYNGO-ESOPHAGEAL DIVERTICULA

where the diverticulum bulges to the right, when the right-sided approach is preferred. An oblique incision is made along the anterior border of the sternocleidomastoid muscle. This incision is deepened through the platysma muscle. The omohyoid muscle is exposed and retracted downwards and medially. The sternomastoid muscle is retracted posteriorly. The left lobe of the thyroid and the overlying sternohyoid muscle are then retracted medially. The inferior thyroid vessels are usually encountered. If they interfere with the exposure,

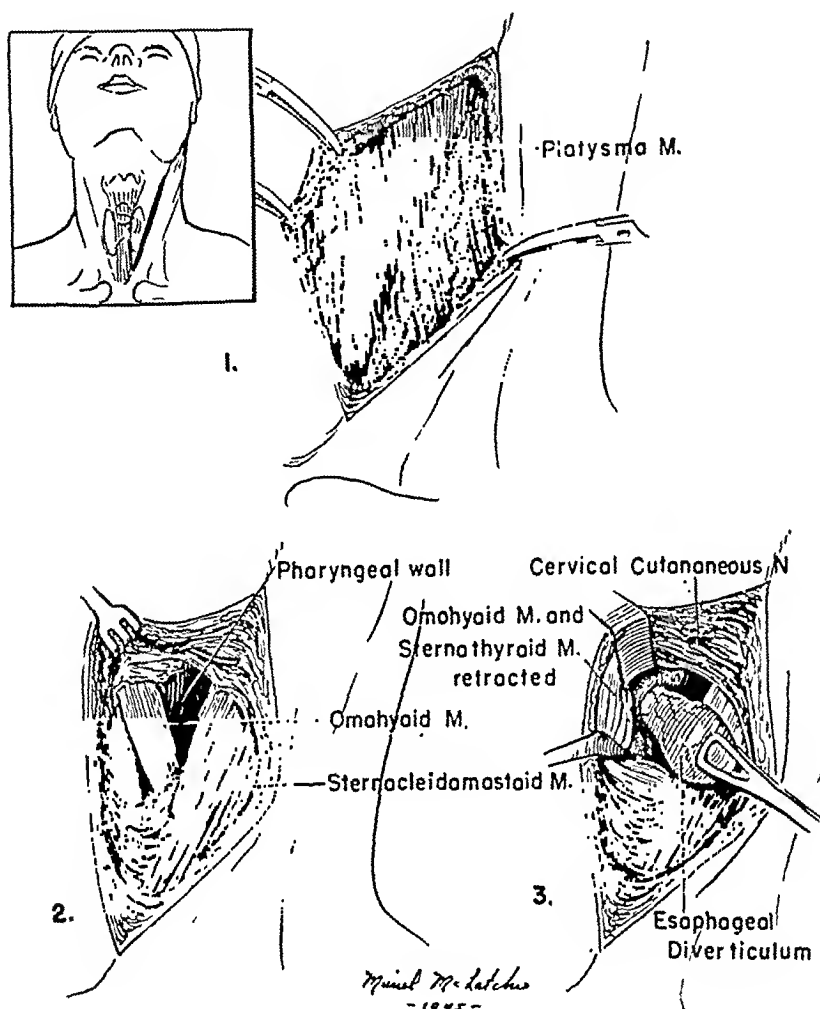


FIG. 1.—Diagram to show the position of the incision (inset) and the stages of dissection. (1) Skin incision retracted exposing the platysma muscle. (2) Cut-edges of skin and platysma muscle retracted exposing the omohyoid muscle, the sternocleidomastoid muscle, and the lateral wall of the pharynx. (3) Diverticulum completely freed and drawn out of the wound in preparation for excision.

they are divided between silk ligatures. The carotid sheath and its contents are retracted laterally. By blunt dissection with the scissors the retropharyngeal space is entered and by enlarging the dissection downwards in this plane the diverticulum can be found with ease. Gentle dissection frees the fundus of the diverticulum which can then be grasped with a forceps and drawn through the wound. The neck of the sac is developed carefully. In doing this

a small artery is usually found extending from the pharyngeal wall onto the posterior surface of the diverticulum. This should be tied and cut.

The removal of the diverticulum is now begun. A serious objection to some of the methods of removal which have been advocated is that the diverticulum

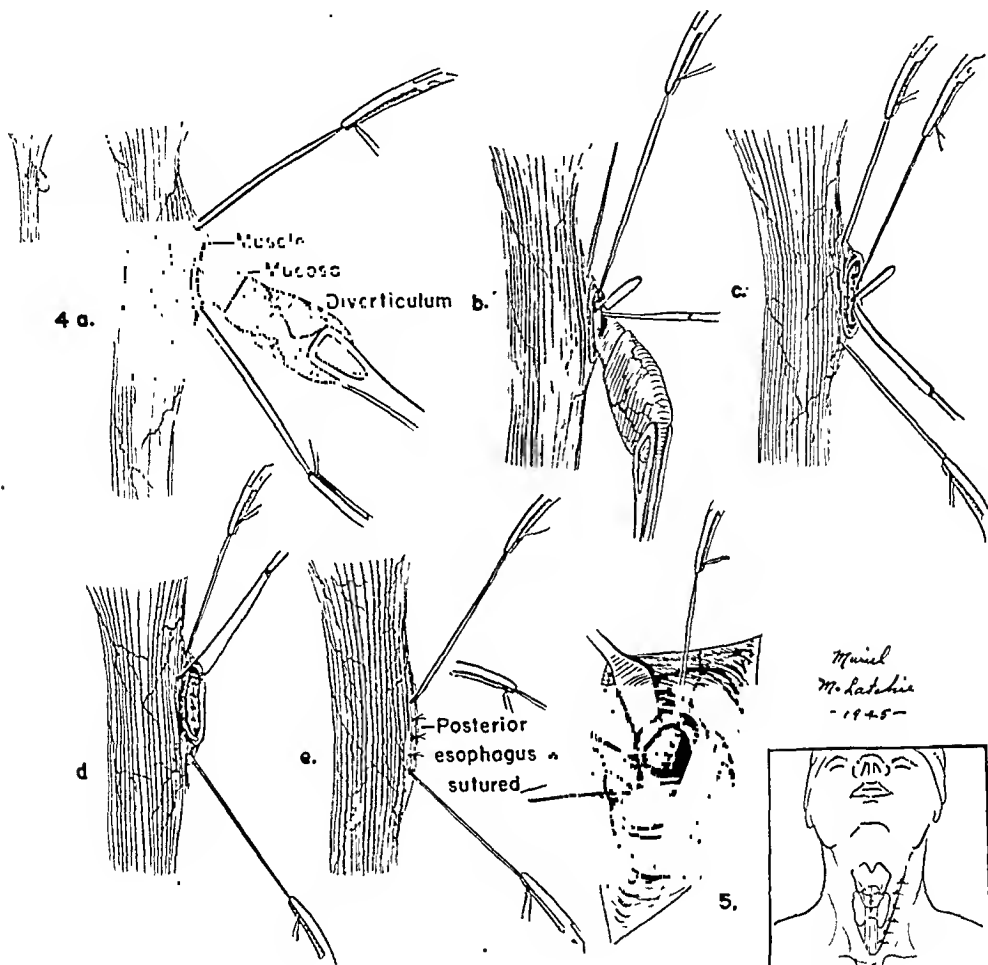


FIG. 2.—Diagram to illustrate the steps of excision of the diverticulum and the closure of the resulting defect. (4a) Incision through the muscular layer completed. Mucosa not yet cut, stay-sutures at upper and lower ends of muscle incision. Note retraction of muscularis. (b) Incision of the mucosa begun. First mucosal suture tied; second suture placed but not yet tied. (c) Diverticulum removed; mucosal suture continued. (d) Closure of mucosal layer completed; first muscle layer suture placed but not tied. (e) Closure of muscle layer completed. (5) *In situ* view of the field of operation before closure of the wound.

Inset: Operation complete. No drain.

was tied at its base and inverted into the wall of the esophagus with a purse-string suture. To avoid this unnecessarily clumsy method, the diverticulum may be cut at its base and the resulting defect closed in two layers with interrupted fine silk sutures. This eliminates the presence of a stump of tissue which inevitably becomes necrotic, and avoids the danger of constricting the esophageal lumen by substituting a neatly closed vertical incision for the

bunched-up wall at the site of inversion of the tied-off stump. An important detail of technic in this step of the procedure is to cut through the outer layers of the diverticulum an appreciable distance from its base where it joins the pharyngeal wall. This makes allowance for the unavoidable tendency of the muscularis to retract. If this precaution were not observed, the edges might separate so widely that too much tension would be required to approximate them and proper healing might be interfered with. After circumcising the muscular coat of the diverticulum near its base, stay-sutures of fine silk are placed, one at each end through the muscularis (Fig. 2, 4A). The incision of the mucosa is then begun and after cutting it through part way, the first mucosal suture is placed and tied. Using this stitch for traction, the remainder of the mucosa is cut and the approximation of the two mucosal edges is completed using interrupted fine silk sutures placed in such a way that the knots are tied on the lumen side. No effort is made to invert the edges. If the incision through the muscularis has been properly placed, the edges of the muscular layer can now be approximated with fine silk sutures without any tension (Fig. 2). After closure of the muscular layer has been completed, the stay sutures at each end are withdrawn and the esophagus and pharynx are allowed to drop back into place.

The left lobe of the thyroid and the omohyoid and sternocleidomastoid muscles are then allowed to resume their normal position and the wound is closed with a layer of fine silk sutures in the platysma muscle and a second layer in the skin.

POSTOPERATIVE MANAGEMENT

The patient is allowed to be out of bed on the day after that of the operation. On that day also a few sips of water or normal saline solution are allowed each hour to prevent excessive dryness of the mouth. The necessary amount of fluid containing glucose and saline as indicated is administered by venoclysis. Sulfadiazine is given intravenously, usually 2.5 grams per 24 hours for approximately three days. The administration of penicillin is continued for approximately five days. Liquid food is allowed sparingly on the third day and the amount gradually increased during the next few days. Soft solids are given cautiously by the end of one week and from then on the amount and kind of solid foods are rapidly increased. A normal diet can be taken by the end of two weeks. The patient is usually ready for discharge from the hospital by the tenth postoperative day.

RESULTS

Although the number of cases is small (five in all), the complete freedom from complications of any sort suggests that this one-stage operation is worthy of further trial. The average stay in the hospital after the performance of the operation has been 11 days. Two illustrative case reports are submitted.

CASE REPORTS

Case 1.—M. G. H. No. 477674: W. G., female, age 75, was admitted to the Baker Memorial Hospital on January 25, 1945. She had first learned that she had a pouch in

her esophagus eight or nine years previously. It appeared to have increased in size until at the time of admission it would fill up enough to interfere with her voice and her swallowing. She could regurgitate food from the pouch. She was otherwise asymptomatic.

Physical examination showed a thin, frail-appearing, very active woman. Examination was entirely negative. There were no palpable masses in the throat and no audible gurgling. Blood pressure 100/65.



FIG. 3.—Case 1: Roentgenogram showing a large pulsion diverticulum of the pharyngo-esophageal junction extending into the superior mediastinum.

Laboratory studies revealed a white blood count of 6800, photo hemoglobin of 10.7 Gm. The serum protein was 6.4 mg. per cent and the nonprotein nitrogen 27.0 mg. per cent.

Penicillin throat spray was administered every two hours beginning on January 28. Penicillin for intramuscular use as a prophylactic treatment was not available for civilians at that time. Intravenous sulfadiazine was begun on the day of operation and continued for five days.

On January 30, the diverticulum of the esophagus was excised in one stage. An incision was made along the anterior border of the sternocleidomastoid muscle in the left

side of the neck. The platysma muscle was incised and one or two superficial veins were tied and cut. It was not necessary to divide the omohyoid muscle or the inferior thyroid artery. The diverticulum was found readily. It was a rather large one with a large opening. It was removed and the layers of the posterior pharyngeal wall were approximated with fine silk. The sutures in the mucosal layer were tied on the inside. The edges of the muscularis were then approximated and a third layer of sutures was used to roll the sutured portion in. Because of the difficulty of securing a perfectly dry field, a drain was brought out through the lower end of the incision, to be removed in 24 hours, and the wound was closed with silk.



FIG. 4.—Case 2: Roentgenogram showing a medium-sized pulsion diverticulum of the pharyngo-esophageal junction. Oblique view showing orifice of the sac.

Pathologic examination of the specimen showed a soft, gray-red sac, measuring 4.0 x 2.5 x 1.0 cm. The serosa was injected. The inner lining of the sac was made up of soft, gray, glistening, plicated mucosa. A 1-cm. area of the mucosa was dark gray and mottled with discrete spots of injection, but there was no induration. The wall of the sac measured up to 2 mm., but there was thickening of the distal wall up to 5 mm.

The patient's postoperative course was uneventful. The wick was removed on the day following operation and the sutures were removed eight days after operation. She was discharged from the hospital in excellent condition, with the wound well healed on February 12.

Case 2.—M. G. H. No. 504276: J. R., male, age 47, was admitted to the Baker

Memorial Hospital on September 17, 1945. He had first noticed about four years previously that when he bent his neck or leaned forward, particles of previously eaten food appeared in his mouth. He was conscious of excessive mucus in his throat at night. There was no choking, however, or difficulty in breathing. Sometime after this he began to cough up food and have difficulty in swallowing large mouthfuls. A roentgenologic examination in 1944 had been negative, but, in July, 1945, a diagnosis of diverticulum of the esophagus had been made.

Physical examination was entirely negative. The patient was a well-developed and well-nourished man. Blood pressure 114/68.

Laboratory studies revealed a white blood count of 9900, photo. hemoglobin of 14.7 Gm. The serum protein was 6.9 mg. per cent and the nonprotein nitrogen 27 mg. per cent.

Intramuscular injections of penicillin were begun on the day of admission. The administration of sulfadiazine was likewise started on the day of admission, but the drug was omitted two days later because the patient developed a skin rash.

On September 20, 1945, the esophageal diverticulum was excised. An oblique incision was made in the left side of the neck along the anterior border of the sternomastoid muscle and deepened through the platysma muscle. The omohyoid muscle was retracted downwards. The retropharyngeal space was entered. The diverticulum was found easily. It lay in the usual location. It was of medium size. There was no evidence of inflammatory reaction around it. It was freed up and traction made upon it. The muscularis close to its base was incised exposing the mucosa which was then cut. The mucosal edges were sutured with interrupted No. 3 silk with the knots tied on the inside. The diverticulum was finally removed and the closure of the pharyngeal wall was completed with a single layer of fine silk sutures to approximate the muscular edges. There was almost no bleeding and it was, therefore, decided to close the wound without drainage. This was done using fine silk sutures in the platysma and subcutaneous fat and silk in the skin.

Pathologic examination of the specimen revealed a previously opened sac 2 cm. in diameter with a smooth gray outer surface. The wall was 1 mm. thick. There was a small amount of friable red tissue in the lumen.

The patient's postoperative course was uneventful. He was up out of bed on the 2nd day following operation, the stitches were removed on the 4th day, he was started on a soft solid diet on the 7th day, and discharged from the hospital in excellent condition with the wound well healed on the 9th postoperative day. He reported for examination on October 15th, and was completely symptom-free and ready to return to work.

CONCLUSIONS

Although the two-stage operation for the removal of pulsion diverticulum of the pharyngo-esophageal junction represented a definite improvement over the earlier technics used in the performance of the operation in one stage, it is now possible, by observing certain refinements of technic, herein described, and by taking advantage of the protection against infection which results from the prophylactic use of penicillin and sulfadiazine, once more to resume the use of a one-stage procedure which has obvious advantages over the two-stage operation.

REFERENCES

- 1 Mayo, C. H.: Diagnosis and Treatment of Esophageal Diverticula. *ANNALS OF SURGERY*, 51, 812, 1910.
- 2 Mayo, C. H.: Treatment of Diverticulum of Esophagus. *ANNALS OF SURGERY*, 77, 267, 1923.
- 3 Lahey, F. H.: Esophageal Diverticula. *Arch. Surg.*, 41, 1118, 1940.
- 4 Harrington, S. W.: Pulsion Diverticulum of the Hypopharynx at the Pharyngo-esophageal Junction. *Surgery*, 18, 66, 1945.

ANATOMIC DATA REGARDING THE SURGICAL TREATMENT OF ANGINA PECTORIS

GENO SACCOMANNO, PH.D.

INSTRUCTOR OF PATHOLOGY

LT. (J.G.) ROBERT A. UTTERBACK, M.C., U.S.N.R.,

AND

ROLAND M. KLEMME, M.D.

PROFESSOR OF SURGERY

ST. LOUIS, MO.

FROM THE DIVISION OF NEUROSURGERY, ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, MO.

SURGICAL PROCEDURES devised for relief of pain of cardiac origin have involved extensive interruption of preganglionic or postganglionic nerve fibers.^{1, 2, 3} This has been accomplished either by section of the white communicating rami of the upper thoracic spinal nerves or by removal of the inferior cervical and upper thoracic sympathetic trunk. Injection of this portion of the sympathetic trunk with alcohol, also, is an accepted method. All these attempts, apparently, have been made without complete or proven anatomic and physiologic evidence of the exact origin of the preganglionic and postganglionic sympathetic neurons or of the exact course taken by the afferent pain fibers of spinal ganglion origin which accompany these sympathetic nerve complexes. Thus, the exact origin of the preganglionic sympathetic fibers which accelerate the heart and dilate or constrict the coronary arteries is of more practical interest than is at first apparent. It is known that all of the cardiac accelerator fibers have their preganglionic origin in the upper thoracic segments. These preganglionic fibers effect synaptic connections with postganglionic neurons in both the cervical and thoracic sympathetic ganglions, and the postganglionics reach the heart *via* the cervical and thoracic cardiac nerves. Cardiac afferent (pain) fibers of spinal ganglion origin accompany the sympathetic cardiac nerves to enter the spinal cord in the upper thoracic region; other cardiac afferent fibers are components of the vagus nerve.

It is the object of this investigation to determine the exact origin of the preganglionic cardiac accelerator fibers. This was done with the aid of a series of experimental procedures involving direct stimulation of the nerve trunks and roots as they issue from the thoracic spinal cord.

METHOD

Dogs were used as the experimental animals. Under nembutal anesthesia, a laminectomy was performed extending from the seventh cervical to the sixth or seventh thoracic segments. The spinal cord was transected at approximately the eighth cervical segment and again at the seventh thoracic level. The spinal nerves were isolated and a ligature was placed on each nerve at the point of its emergence from the dura. Each nerve was then cut proximal to the ligature

and the length of spinal cord thus separated from its attachments was removed from the body.

A common carotid artery was cannulated and attached to a mercury manometer in such a way as to record variations in pulse rate and blood pressure on a kymograph.

Each spinal nerve, in turn, was picked up, carefully separated from surrounding tissues, its excess moisture removed with a small absorbent cotton

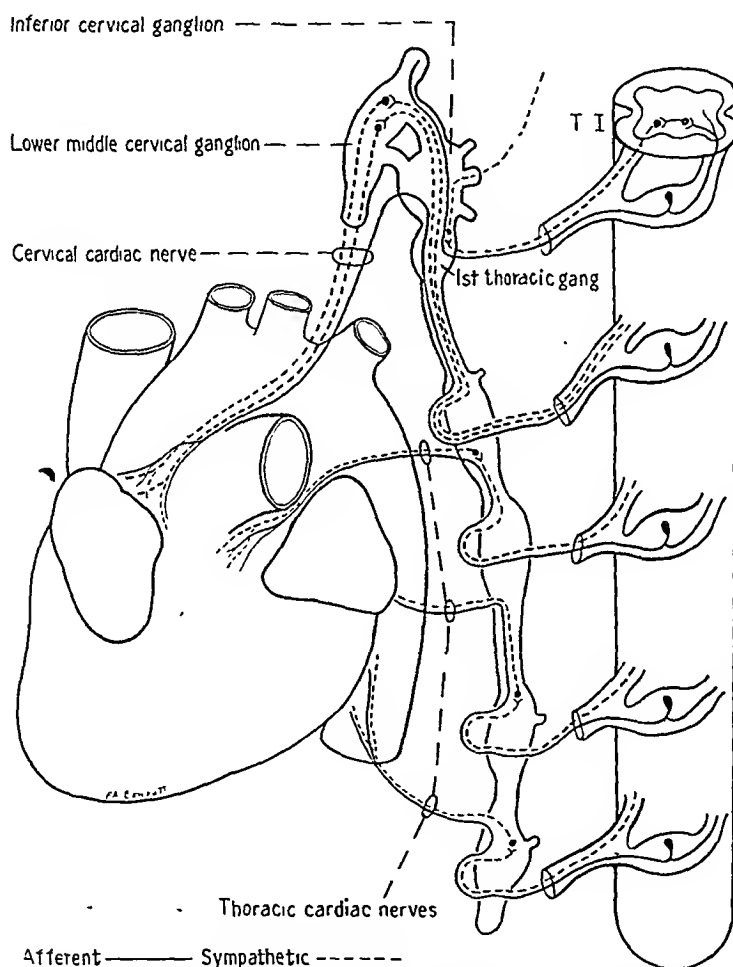


FIG. 1.—Diagrammatic drawing illustrating distribution of sympathetic cardiac accelerator and afferent (pain) fibers.

applicator, and then stimulated with varying strengths of faradic current from a Harvard Inductorium. A coil setting of eight to nine centimeters was found to give the most adequate stimulus. Sufficient time was allowed between successive stimulations for the pulse rate and blood pressure to return to the control level.

At the end of each experiment the segmental origin of every nerve involved in the experiment was confirmed by dissection.

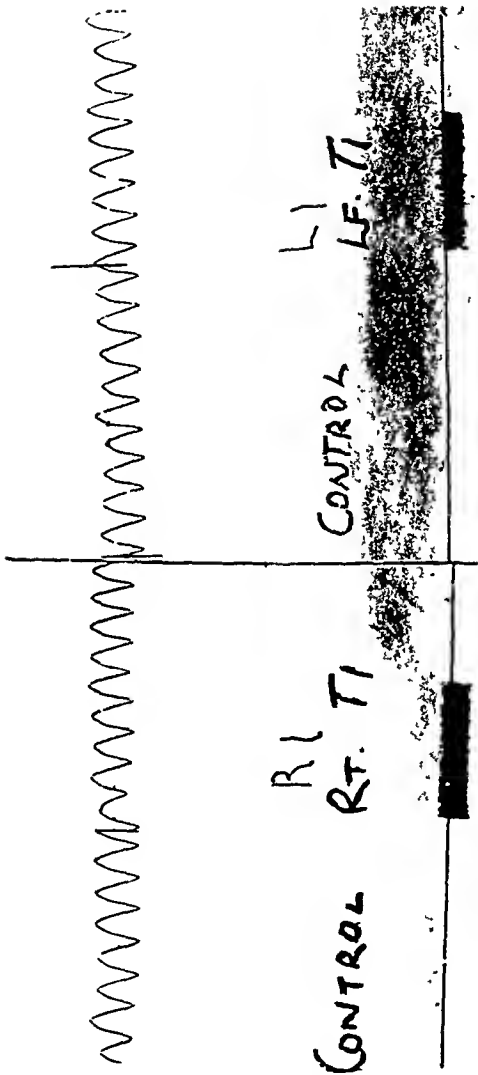


FIG. 2.—Kymographic record showing carotid blood pressure and heart rate changes following faradic stimulation of the first thoracic nerve trunks.

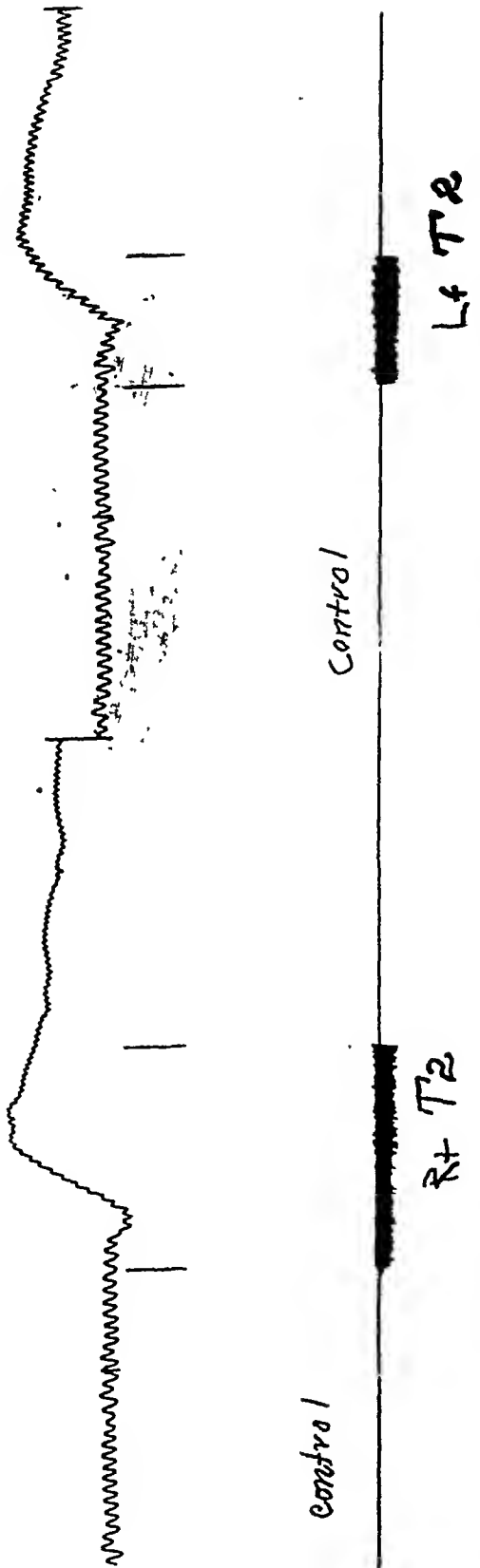


FIG. 3.—Kymographic record showing carotid blood pressure and heart rate changes following faradic stimulation of the second thoracic nerve trunks.

EXPERIMENTAL FINDINGS

In every animal tested it was found that stimulation of the eighth cervical or the first thoracic spinal nerve failed to elicit any perceptible influence on either the pulse rate or the blood pressure (Fig. 2). This suggests that, if any preganglionic fibers arise from the first thoracic segment and pass through the first white communicating ramus to effect synaptic connections in the sympathetic trunk with postganglionic neurons which reach the heart, they are not numerous enough to elicit a cardiac response under the conditions of the experiment. Increased and decreased strength of stimulus also failed to elicit a response.

In view of these findings, it may be concluded that very few, if any, of the preganglionic fibers of the first thoracic segment are cardiac accelerator fibers.

In the second thoracic nerve, however, the weakest effective stimulus

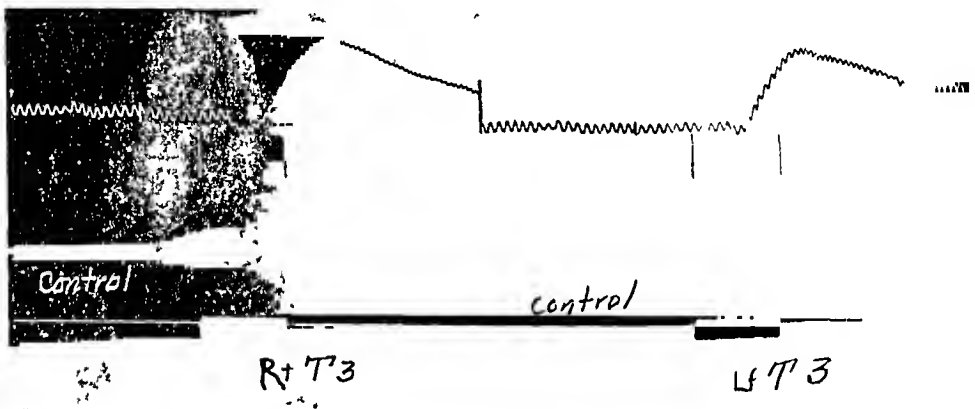


FIG. 4.—Kymographic record showing carotid blood pressure and heart rate changes following faradic stimulation of the third thoracic nerve trunks.

elicited a very marked rise in blood pressure and an equally striking acceleration of pulse rate (Fig. 3). The response from the third thoracic nerve was of approximately identical strength and duration (Fig. 4). Stimulation of the fourth, fifth and sixth thoracic nerves resulted in progressively diminishing acceleration effects, but the effect on blood pressure elevation was remarkably consistent at all these levels (Figs. 5 and 6). The constant pressure response probably is due to stimulation of the splanchnic nerves. These preganglionic neurons are present in the spinal nerves from the fourth or fifth through the twelfth thoracic segments, and upon stimulation are thought to elevate systemic blood pressure by constricting the vessels of the so-called "splanchnic bed."

In the first series of experiments the spinal nerves were isolated and stimulated on only one side in each animal. In some of these animals the stimulation was carried out on the left side; in others on the right. Comparison of the records revealed very plainly that in those animals whose left spinal nerves were stimulated the rise in blood pressure was much more striking than the

acceleration of the pulse rate; in those whose right spinal nerves were stimulated the acceleration of pulse rate was marked but there was only a slight rise in blood pressure. In two animals the spinal nerves on both sides were isolated at the same time and subjected to stimulation. In these experiments it was found that this same difference in reaction was present on the two sides of the same animal and, thus, was not simply a variation in reaction from animal to animal nor the result of slight difference in technic (Figs. 4 and 5).

To investigate any possible effect of antidromic conduction the sensory and motor roots were separated in one animal and stimulated separately. Stimulation of the sensory root failed to elicit any response, while stimulation of the motor root alone produced a response identical with that resulting from stimulation of the whole spinal nerve (Fig. 7).

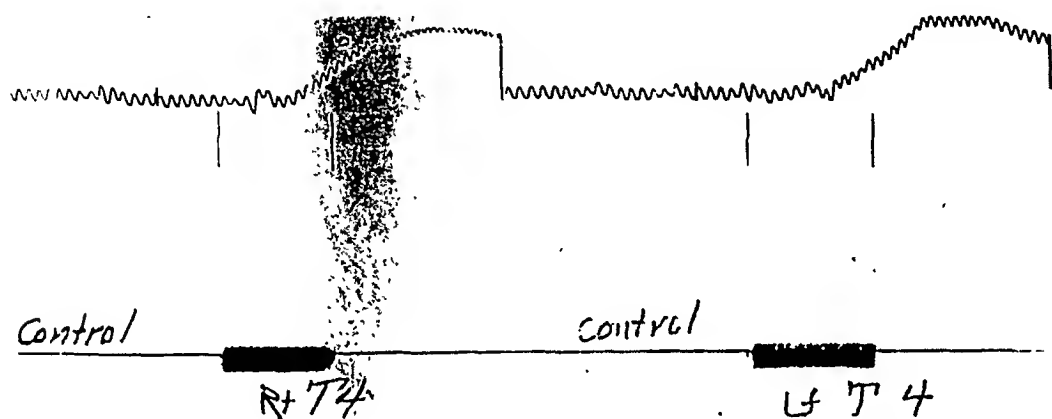


FIG. 5.—Kymographic record showing carotid blood pressure and heart rate changes following faradic stimulation of the fourth thoracic nerve trunks.

DISCUSSION.—In the present series of experiments stimulation of the roots of the second to the sixth thoracic nerve roots readily elicited both cardiac acceleration and increased carotid pressure, but stimulation of the eighth cervical and first thoracic spinal nerves failed to elicit any change in heart rate or carotid pressure. These results apparently indicate that the first thoracic nerve conveys no preganglionic cardiac accelerator fibers (Fig. 1).

Unpublished anatomic evidence derived from a series of experiments intended to determine the exact course of afferent cardiac fibers which accompany the cervical and thoracic cardiac sympathetic nerves indicates that most of the afferent fibers of spinal ganglion origin descend in the sympathetic trunk to enter the thoracic spinal nerves through communicating rami below the first thoracic segments. Apparently, then, the afferent fibers from the heart take the same course as the efferent sympathetic cardiac accelerator fibers; that is, none of them pass through the first gray or white communicating rami.

The marked difference in response to stimulation of the left and the right cardiac sympathetic nerves confirms a portion of the findings reported by Fogelson.⁴ This investigator noted that, although the cardiac sympathetic

nerves on either side had the combined effect of accelerating the heart rate and raising the blood pressure, stimulation of the right cardiac sympathetics elicited a greater acceleration response, while stimulation of the left cardiac sympathetics influenced principally the volume of ventricular output.

Anrep and Segall,⁵ in an apparently excellent investigation on cardiac physiology, advanced the opinion that sympathetic cardiac acceleration is accompanied by coronary vasodilatation. This conclusion seems logical, but subsequent studies afford overwhelming evidence in favor of the opposite view—namely, that stimulation of the sympathetic system, though it accelerates the heart rate, causes an increase in the tone of coronary vessels.

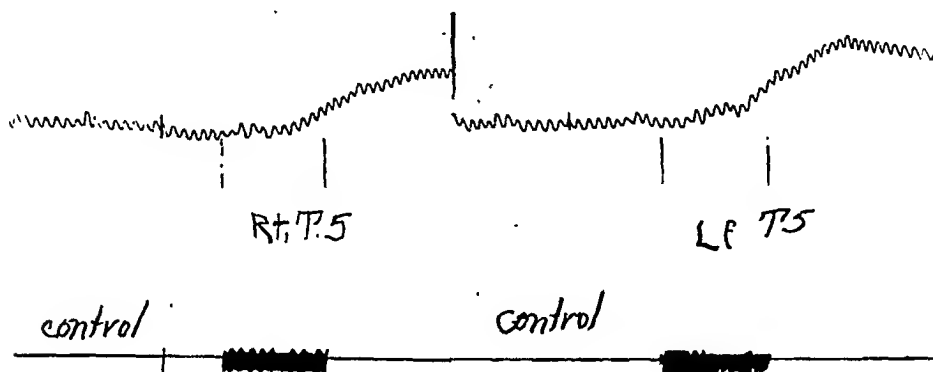


FIG. 6.—Kymographic record showing carotid blood pressure and heart rate changes following faradic stimulation of the fifth thoracic nerve trunks.

Kountz, Pearson and Koenig,⁶ in experiments with revived human hearts, found that when the heart was beating strongly and with the normal A-V association, stimulation of the inferior cervical ganglion reduced the flow into the coronary arteries at the same time it increased the heart rate. Only when there was dissociation of atrial and ventricular contractions did sympathetic stimulation increase the coronary flow. Under this latter circumstance, ventricular rate was unchanged by sympathetic stimulation.

Katz and Jochim,⁷ in their experiments with isolated dog hearts, concluded that sympathetic nerves carry both adrenergic vasodilator and vasoconstrictor fibers, with the latter predominant. They also observed that when the spinal cord was cut to release the sympathetic system from central nervous system influence there resulted a definite coronary vasodilatation, thus, strongly implying that tonic constriction is mediated *via* sympathetic fibers of the same origin as those which carry accelerator impulses. They concluded that if the coronary innervation in man is similar to that in the dog, then sympathetic denervation in man may not only interrupt afferent pain fibers, but the only efferent vasoconstrictor fibers as well.

Raney⁸ states that, whether the sympathetic postganglionic fibers constrict or dilate the coronary vessels normally, it is very probably that their action in

certain pathologic states of the vessel walls is to constrict the vessels so markedly as to produce ischemia of the cardiac muscle.

All of the literature to date, then, seems to indicate that the interruption of sympathetic accelerator and vasomotor fibers, and afferent fibers of spinal ganglion origin, would bring about an increase in coronary blood flow and at the same time materially lessen the pain of any subsequent anginal attacks. Since the sympathetic cardiac acceleration fibers and cardiac afferent fibers of spinal ganglion origin have no anatomic relationship with the first thoracic nerve, probably most sympathetic coronary vasomotor fibers also arise below the first thoracic nerve. If this is the case, then section of the sympathetic trunk below the first thoracic sympathetic ganglion with removal of the second, third

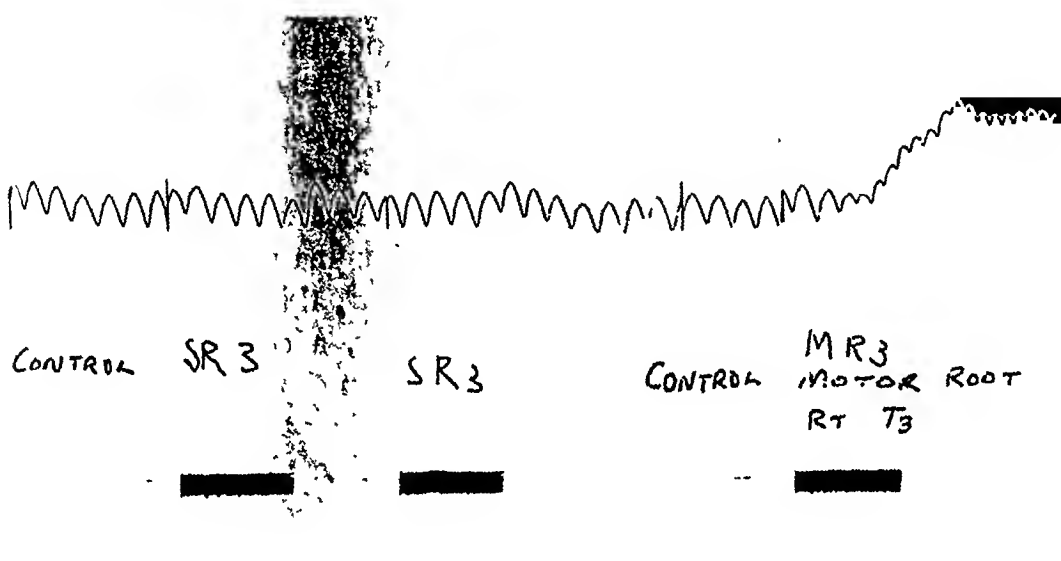


FIG. 7.—Kymographic record showing carotid blood pressure and heart rate following faradic stimulation of the right third thoracic sensory root (SR. 3.) followed by stimulation of the motor root (MR. 3.) of the same segment.

and fourth sympathetic ganglions would result in complete denervation of the heart. Carefully controlled alcohol injection of the second, third and fourth sympathetic ganglions would produce the same results with less surgical trauma. Since the pain of anginal attacks is usually unilateral and on the left side, thoracic sympathetic ganglionectomy on that one side only should result in favorable relief of pain and cardiac ischemia.

Raney⁵ has described a series of operations for angina in which he has used a procedure virtually identical with the one we would suggest if anatomic and physiologic conditions in man are similar to those of the dog. He reports 100 per cent relief in all 11 of the patients so treated.

From our findings, we believe that either extirpation or alcohol injection of the second to the fifth thoracic sympathetic ganglions on the affected side only would result in complete or marked alleviation of coronary spasm and virtually complete relief from pain in subsequent anginal attacks. Concluding, from our experiments, that the eighth cervical and first thoracic segments do not contribute to cardiac innervation, it, thus, becomes apparent that effective cardiac

denervation may be achieved without disturbing the inferior cervical and first thoracic ganglions and their communicating rami—in this way leaving intact part of the pathways for sympathetic responses in the head, neck and upper extremity.

SUMMARY

In dogs from which a length of spinal cord had been removed, stimulation of the isolated spinal nerves was observed to produce cardiac acceleration and a rise in systemic blood pressure when the second through the sixth thoracic spinal nerves were stimulated. No change in heart rate or blood pressure was observed when the eighth cervical or first thoracic spinal nerves were stimulated, indicating that these segments do not convey any cardiac efferent fibers.

The effect in pulse rate was most marked in the second and third thoracic nerves, with diminishing effect in the fourth and fifth and only very slight effect below the fifth thoracic nerve. The effect on systemic blood pressure was more or less constant from the second thoracic down as far as the seventh thoracic nerve.

Attention is called to the implications of this information as the anatomic basis for a more scientific surgical treatment of angina pectoris. By means of surgical removal or alcohol injection of the second, third and fourth thoracic sympathetic ganglions on the affected side only, a complete alleviation of anginal pain and a reduction of coronary vasospasm should result. This single surgical procedure does not completely interrupt the pathways of sympathetic effector impulses to the head and upper extremity, since the first thoracic segment which conveys fibers to these areas, but which does not convey cardiac afferent or efferent fibers, remains intact.

REFERENCES

- ¹ Janesco, T.: Surgical Treatment of Angina Pectoris. *Bul. de l'Acad. de Med.*, **86**, 67, 1921.
- ² Braeucker, W.: Die chirurgische Behandlung der Angina Pectoris. *Arch. f. Klin. Chir.*, **117**, 664, 1933.
- ³ White, J. C.: Angina Pectoris. *Am. Jour. Surg.*, **9**, 98, 1930.
- ⁴ Fogelson, L. J.: Die Wirkung der extrakardialen Nerven auf das Herz, vor und nach der ausschaltung des Sinus knotens. *Ztschr. f. d. ges. exp. Med.*, **68**, 145, 1929.
- ⁵ Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation. *Heart*, **13**, 239, 1926.
- ⁶ Kountz, W. B., Pearson, E. F., and Koenig, K. F.: Observations on the Effect of Vagus and Sympathetic Stimulation on the Coronary Flow of the Revived Human Heart. *Jour. Clin. Invest.*, **13**, 1065, 1934.
- ⁷ Katz, L. N., and Jochim, K.: Innervation of Coronary Vessels of Dog. *Am. J. Physiol.*, **126**, 395, 1939.
- ⁸ Raney, R. B.: A Hitherto Undescribed Surgical Procedure Relieving Attacks of Angina Pectoris. *J. A. M. A.*, **113**, 1619, 1939.

A TEN-YEAR SURVEY OF INTESTINAL OBSTRUCTION

E. L. ELIASON, M.D., AND ROBERT F. WELTY, M.D.

PHILADELPHIA, PA.

FROM THE SERVICE OF DR. E. L. ELIASON, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

RECENTLY a review was carried out of all cases in which the diagnosis of intestinal obstruction was made on the Service of the senior author at the Hospital of the University of Pennsylvania during the ten-year period, 1934-1943. It was hoped that two things could be accomplished by such a survey. First, certain well-recognized features of intestinal obstruction could be reëmphasized, *e.g.*, the high mortality associated with strangulation, advanced age, delayed treatment, *etc.* Second, we hoped to obtain statistical evidence to support a clinical impression that the mortality in intestinal obstruction has been reduced in the past ten years by improved treatment, the use of intestinal suction-drainage by means of the Miller-Abbott tube being an important factor. During this ten-year period, there were 292 cases who were admitted with either the primary diagnosis of obstruction or who developed this as a complication during their hospitalization. The importance of intestinal obstruction is demonstrated by the fact that 17 per cent of all surgical deaths at the Philadelphia General Hospital resulted from this condition.

In our survey the youngest patient was six weeks old, the oldest 84 years. Chart I shows the distribution by decades. The average age of all 292 cases was 45 years. Of the group who survived, the average age was 44 years, of those who died, 59—a difference of 15 years. This bears out the fact that the older patient with intestinal obstruction has a poorer chance for survival than the younger one. Carcinoma accounts for a high percentage of cases of obstruction in the older age-group. The nature of the disease in itself contributes further to the increased mortality in this group.

The cases were about equally divided between males and females, 48 per cent and 52 per cent, respectively (Table I). However, the mortality among the males was 14 per cent and among the females 9 per cent. The higher mortality in the former group is to be explained in part at least by the cases of lymphopathia venereum. Though this disease accounted for many cases of obstruction among the females, no deaths resulted from it, and during this period no cases of rectal stricture attributable to this disease were seen in the male.

A little more than half (60 per cent) were only partially obstructed (Table II). The mortality in this group, however, 10 per cent, was only slightly lower than in those who had complete obstruction, 12 per cent. One might have anticipated a lower mortality in those only partially obstructed, but, once again, the mortality in this group was increased because of the cases of carcinoma included therein. The cases were quite evenly divided between those in whom the disease was acute and those in whom it was chronic (Table III). The mortality in the two groups was exactly the same, 11 per cent, which corre-

sponded to the mortality for the entire series of 292. The nature of one of the important etiologic factors in chronic obstruction, *i.e.*, carcinoma, balances the seriousness of acute obstruction.

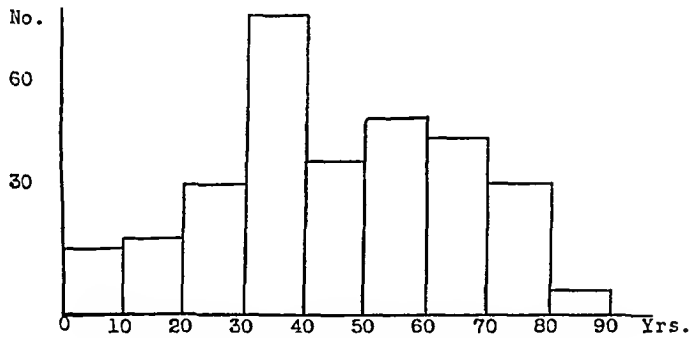


CHART I.—Distribution of cases by decades.

In the acute series, the average duration of symptoms for those who died was 2.6 days and for those who lived, 2.3 days (Table IV). There is no significant difference between these two figures. This is at variance with the

TABLE I

SEX		No.	Died	Mortality
Females....	..	153 (52%)	13	9%
Males...	..	139 (48%)	19	14%

TABLE II

DEGREE OF OBSTRUCTION		No.	Died	Mortality
Partial..	..	176 (60%)	18	10%
Complete	..	116 (40%)	14	12%

TABLE III

DURATION OF SYMPTOMS		No.	Died	Mortality
Acute.....	..	153 (52%)	17	11%
Chronic.....	..	139 (48%)	15	11%

generally accepted fact that the mortality for a group of cases with delayed treatment is higher than in a similar group with early treatment. About ten years ago a review of intestinal obstruction similar to this one was carried out at the Hospital of the University of Pennsylvania. Comparable figures obtained in the earlier survey showed that the average duration of the disease in those who died was 2.1 days and in those who lived, 1.2 days, a result which would be anticipated. In comparing the figures in these two series one may be justified in inferring that some cases with delayed treatment are now being salvaged who previously would have died. As more and more cases are saved

INTESTINAL OBSTRUCTION

in spite of delayed treatment, the average duration of symptoms for those surviving will increase and tend to make this figure approach more closely that of the group in whom death results. The average delay of 2.5 days before hospitalization in this series is still too long and unnecessarily increases the mortality in acute obstruction. Unfortunately, delay sometimes occurs even after admission to the hospital. In the face of a typical history and findings on

TABLE IV
ACUTE CASES

AVERAGE DURATION OF SYMPTOMS

	Previous Series	Present Series
Lived.....	1.2 days	2.3 days
Died.....	2.1 days	2.6 days

TABLE V
SITE OF OBSTRUCTION*

	No.	Died	Mortality
Small bowel.....	184	14	8%
Large bowel.....	114	18	16%

* Some cases showed multiple points of obstruction.

TABLE VI
CAUSE OF OBSTRUCTION

	No.	Died	Mortality
Adhesions.....	79 (27%)	4	5%
Malignancy.....	59 (20%)	20	34%
Lymphopathia venereum.....	41 (14%)	0	0%
Inguinal hernia.....	41 (14%)	2	5%
Femoral hernia.....	13 (4%)	4	31%
Ventral hernia.....	8 (3%)	0	0%
Internal hernia.....	5 (2%)	1	20%
Others.....	46 (16%)	1	2%

physical examination suggesting intestinal obstruction, one should not defer treatment if a typical roentgenogram is not found. The burden of the diagnosis and the resultant decision as to treatment should not be placed solely on the roentgenologist.

The mortality for those having small bowel obstruction, 8 per cent, was only half that in which the large bowel was involved, 16 per cent (Table V). Carcinoma of the large intestine no doubt accounts for the higher mortality in the latter group.

The commonest causes for obstruction were adhesions, malignancy, and hernia, accounting for 63 per cent of the cases (Table VI). The differences in mortality among the various groups were striking. Malignancy accounted for 20 per cent of the cases of obstruction, and 34 per cent of these died. Adhesions accounted for 27 per cent of the cases in this series, but only 5 per cent of these died. One should not infer from these figures that the mortality during this period for carcinoma of the large bowel was 34 per cent. Many

cases with this disease were admitted without evidence of significant obstruction and do not, therefore, appear in this collection.

Of the 292 cases in this series, 33 (11 per cent) were instances of post-operative obstruction.

No case with lymphopathia venereum died. The procedure carried out in this disease was usually a palliative one, such as a simple loop-colostomy or a Lahey-type of colostomy.

TABLE VII
COMPARISON OF CAUSE OF OBSTRUCTION AND MORTALITY

	Per Cent of Series	Per Cent of Deaths
Malignancy.....	20%	63%
Femoral hernia.....	4%	13%
Adhesions.....	27%	13%
Inguinal hernia.....	14%	6%

TABLE VIII
COMPARATIVE MORTALITY OF OLD AND NEW SERIES

Cause	Series	Mortality
Hernia.....	Previous	25.9%
	Present	10%
Adhesions.....	Previous	20.4%
	Present	5%

Twenty-three per cent of the cases were obstructed on the basis of a hernia. The inguinal region was the most common site, and carried a mortality of only 5 per cent. In contrast, the mortality in the femoral hernia group was very high—31 per cent. Failure to recognize promptly the nature of the disease is prone to occur in a femoral hernia, especially if a Richter's-type is present or if the patient is obese. At operation, one should never hesitate to divide the inguinal ligament if necessary to reduce the hernia. Also it is sometimes of value to expose the bowel from above by extending the wound and entering the peritoneal cavity through a muscle-splitting incision. Failure to follow these two suggestions leads at times to unnecessary trauma or rupture of an already strangulated intestine causing further contamination of the peritoneal cavity and increased operative mortality.

Ninety-two per cent of the deaths resulted in cases of obstruction due to malignancy, femoral hernia, inguinal hernia and adhesions (Table VII). Malignancy accounted for 20 per cent of the cases, but 63 per cent of the deaths. Femoral hernia accounted for 4 per cent of the cases, but 13 per cent of the deaths. These two conditions, therefore, were responsible for 24 per cent of the cases of obstruction, but 75 per cent of the deaths.

Comparison of the present series with the previous review of intestinal obstruction at this hospital reveals a definite improvement in the prognosis (Table VIII). In the earlier series the mortality in obstruction due to hernia was 25.9 per cent; in the present series it was 10 per cent. For obstruction due to adhesions, the mortality in the earlier group was 20.4 per cent—in the latter, 5 per cent.

INTESTINAL OBSTRUCTION

Seventy-four cases (25 per cent) showed evidence of strangulation at the time of operation; only 12 per cent of the group died (Table IX). The mortality in similar groups in the previous review ranged from 40-60 per cent. The lower mortality in the present series is related, we feel, to improved methods of treatment and probably also to the fact that the surgery was performed by a relatively small group of men, all with adequate training or supervision. The figure for the Philadelphia General Hospital series, for example, is compiled from statistics on the work of some 50 or 60 surgeons, of varied ages and degrees of experience.

TABLE IX
STRANGULATION

	No.	Died	Mortality
Present series.....	74 (25%)	9	12%
M. G. H.....			40%
N. Y.....			55%
P. G. H.....			60%

TABLE X
MORTALITY

	No.	Died	Mortality
Total.....	292	32	11%
Resected.....	53 (18%)	10	19%

As might be expected, the mortality in that group of cases in which resection was required, was almost double that of the total series, 19 per cent *versus* 11 per cent (Table X).

If one omits the cases of malignancy (which account for 20 of the 32 deaths in this series) and the cases of strangulation (which account for nine of the 32 deaths) then the mortality in the remaining group of 159 cases of obstruction is only 1 per cent (three deaths). The prognosis, therefore, is excellent if a patient is admitted with obstruction, but has no evidence of malignancy or strangulation.

The causes of death are listed in Table XI. Peritonitis, malignancy, pulmonary embolism, pneumonia and cardiovascular-renal disease account for 84 per cent of the deaths. Two of the cases in this series were moribund at the time of admission, and would not respond sufficiently to supportive treatment to permit operation.

Suction drainage of the gastro-intestinal tract by means of the Jutte, Levin or Miller-Abbott tube was carried out in 124 of the 292 cases as an adjunct in the treatment. In general, it has been reserved for the more serious cases. Our clinical impression was that this procedure was of value in 80-90 per cent of the cases in which it was used. Twenty-five per cent of the cases in which suction drainage was carried out required no subsequent operative procedure. Obstruction developing in the postoperative case on the basis of fresh adhesions is a particularly fertile field for correction by intubation without the necessity for subsequent operation.

During the three-year period, 1934-1936, suction drainage was carried out in 26 cases by means of a Jutte or Levin tube placed in the stomach. Eight of these cases succumbed, a mortality of 31 per cent (Table XII). In 1937 the Miller-Abbott tube became available for intubation and decompression of the small intestine. During the seven-year period, 1937-1943, this tube was used in 65 instances of obstruction, with ten deaths, a mortality of 15 per cent. Another 33 cases were treated by gastric suction drainage by means of the

TABLE XI

CAUSE OF DEATH

	No.	Per Cent
Peritonitis	8	25%
Carcinomatosis...	7	22%
Pulmonary embolism....	5	16%
Pneumonia.....	4	13%
Cardiovascular-renal disease..	3	9%
Others.....	5	16%

TABLE XII

SUCTION-DRAINAGE

	No.	Died	Mortality
1934-1936 (prior to M. A. tube).....	26	8	31%
1937-1943 (after M. A. tube)....	98	15	15%

TABLE XIII

TOTAL SERIES

	No.	Died	Mortality
1934-1936 (prior to M. A. tube).....	74	13	18%
1937-1943 (After M. A. tube).....	218	19	9%

Jutte or Levin tube, with five deaths. During this seven-year period, following the introduction of the Miller-Abbott tube, therefore, there were 98 cases in which suction-drainage was used, with a mortality of 15 per cent, in contrast to the mortality of 31 per cent prior to the introduction of the Miller-Abbott tube. The over-all mortality figures for these same periods reflect this drop in mortality also (Table XIII). We would like to point out, again, that suction-drainage is not routinely used in all cases of obstruction, but is reserved for those more serious cases in which it seems indicated. The last figure also shows that the over-all mortality during the last seven years is 9 per cent *versus* 11 per cent for the entire ten-year period, indicating the trend toward continued improvement in mortality in the latter part of this series.

Though a sharp fall in mortality was associated with the introduction of the Miller-Abbott tube, the improvement in prognosis must not be attributed to use of the tube alone.

Though intravenous fluids were available prior to the introduction of the Miller-Abbott tube, the derangement in body chemistry and fluid balance in intestinal obstruction was never as fully appreciated, or combated, as in

recent years. Intravenous fluids are being used more freely than ever before, and repeated determinations of the blood chemistry are carried out to aid in determining the amount and kind of fluids required.

During the period of this survey the blood bank was established at the Hospital of the University of Pennsylvania. As a result, there is a supply of readily available blood and plasma at all times. In cases of strangulation with loss of blood and plasma into the areas of involved intestine, a shock-like picture may result, and the condition of the patient can be much improved by infusions of blood and plasma. Cases requiring prolonged operation or resection of the bowel can be carried through the operation in much better condition if such is administered during the procedure. In cases of prolonged illness, on the basis of partial obstruction or carcinoma, the nutrition of the patient may be poor and the plasma protein and hemoglobin values can be raised by transfusion. The value of transfusion as a tonic in a prolonged illness is not to be overlooked.

During the latter half of this survey, the services of a medical anesthetist were obtained by the hospital, and a program of training residents in anesthesia was introduced. At all times, therefore, we have available anesthesia of the type best suited for the individual case, and the free use of intravenous therapy during operation, under supervision of the anesthetist, is a distinct aid in carrying the patient through the procedure in a more satisfactory condition.

Another factor of great importance in these patients was the introduction of the chemotherapeutic agents—the sulfonamide drugs. They have been of value especially in those cases in which peritonitis from contamination by the fecal stream has been a threat. During the postoperative course they have also been of help in combatting pulmonary infections so that now a postoperative fatality from pneumonia alone is uncommon.

In 18 per cent of the cases in which the Miller-Abbott tube was used we were unsuccessful in getting it to pass into the small intestine. More recently, we have failed in less than 10 per cent. These figures represent the efforts of several people, some of whom have had little experience in passage of the tube. In some of these cases of failure, persistent effort would no doubt have been successful in passing the tube, but the condition of the patient did not justify further delay in operative intervention.

In acute mechanical obstruction, if one is unsuccessful in passing the tube promptly, the question arises as to how long one should persist in the attempt. In general, if one is not successful after six hours, as shown by roentgenographic evidence of progress of the tube, decrease in distention, disappearance of pain, and slower pulse rate, then operation is indicated. If one delays too long in attempts to pass the tube, the patient becomes exhausted, the pulse rate rises and peristalsis disappears. Such a patient has become a poor surgical risk.

In the face of marked distention which cannot be handled by intubation for any reason, a Witzel enterostomy in the left lower quadrant, under local anesthesia and a muscle-splitting incision, still remains the procedure of choice and will give excellent results in most cases. In one report, 86 per cent of the cases of

obstruction following operations for appendicitis were corrected by enterostomy alone.

There is no doubt that the value of the Miller-Abbott tube increases in proportion to the experience and skill of the individual who is passing the tube. One man in the hospital who has had a wide experience in use of this tube has been successful in 75 of the last 76 attempts. The one failure might have been avoided had further delay in operation been warranted. Though passage of the tube can be accomplished in the patient's room, fluoroscopic guidance is a distinct advantage, and often saves much time, since any error in direction of the tube into the duodenum can promptly be corrected. Use of a stylet in the tube or mercury placed in the balloon may aid in more rapid passage of the tube into the duodenum. Once the tip of the tube reaches the second portion of the duodenum, the balloon can be inflated with air and further passage of the tube to the point of obstruction is usually accomplished without difficulty. Occasionally gastric distention recurs while the tube is in the small intestine. This can easily be cared for by placing a Levin tube in the stomach and emptying it by suction. If delay in operation is not justified or if the tube fails to pass and operation is necessary, it is frequently possible during the operation to pass the tube manually from the stomach into the small intestine, and thereby obtain postoperative decompression of the intestinal tract.

At operation, in which a Miller-Abbott tube has been passed, one often finds the small intestine pleated or accordionized on the tube. When removal of the tube is indicated the balloon must be deflated and the tube withdrawn slowly, usually six inches every 15-30 minutes, in order to avoid the possibility of retrograde intussusception.

This tube is a useful adjunct in the treatment of intestinal obstruction but cannot replace surgery in all cases. Certain cases of intestinal obstruction are not candidates for intubation and if used improperly, leading to delay in operation, this maneuver may actually be of harm, giving rise to increased mortality.

Large bowel obstruction requires decompression by operative intervention and should not be attempted by intubation. The Miller-Abbott tube often will not pass into the large bowel, and if it does, the contents of this part of the intestine may be too thick to be drained adequately through the small lumen of the tube. If the ileocecal valve is competent, a closed loop-type of obstruction is present. This is very serious and requires prompt correction. If small bowel distention also is present, this can be handled by intubation. Operative decompression of the large intestine is not thereby avoided, however, and following operation, the small bowel distention is automatically corrected, so intubation in these cases is usually unnecessary.

Strangulation is a strict contraindication to delay in surgery in an attempt to intubate the small intestine. Constant severe pain with exacerbations requiring morphine, tenderness, and perhaps a tender mass, tachycardia and leukocytosis, should be warning signs to prepare the patient for operation as promptly as possible. If the strangulation has progressed to an irreversible

stage, so that resection is necessary, the procedure of choice must be determined at the time of operation—either a double-barrelled enterostomy or primary anastomosis. If primary anastomosis is carried out and the site of repair is under any question, the anastomosis may be temporarily exteriorized or a proximal enterostomy may be performed. A procedure preferable to either one of these, however, we feel, is passage of the Miller-Abbott tube to a point proximal to the site of the anastomosis. Satisfactory decompression of the bowel can be maintained in this fashion and the suture line protected against distention during the early stages of healing. Fluids by mouth can be administered during this time, since the tube will remove all fluid and gas before they reach the site of anastomosis.

SUMMARY

(1) A statistical review of 292 cases of intestinal obstruction is presented.

(2) The average age of those who survived was 44 years, and of those who died, 59 years.

(3) The mortality did not seem to be influenced by whether or not the obstruction was complete or partial, acute or chronic. Improvement in operative technic and pre- and postoperative care probably account for this.

(4) The mortality in small bowel obstruction was one-half that of large bowel obstruction.

(5) Thirty-four per cent of the cases of obstruction due to malignancy succumbed.

(6) Thirty-one per cent of the cases of obstruction due to femoral hernia died. This is in contrast to a mortality of 5 per cent in the cases due to inguinal hernia.

(7) The mortality in the group showing strangulation was only 12 per cent.

(8) If resection is necessary, the mortality is almost doubled.

(9) The over-all mortality in this series was 11 per cent. If the cases of malignancy and strangulation are excluded, the mortality in the remaining 159 cases in this series is 1 per cent.

(10) Following the introduction of the Miller-Abbott tube, the mortality in this series was reduced by one-half. Other factors, including transfusion, chemotherapy and improvement in anesthesia, unquestionably, contributed to this decrease in mortality.

TRAUMATIC PANCREATITIS*

THOMAS A. SHALLOW, M.D., AND FREDERICK B. WAGNER, JR., M.D.
PHILADELPHIA, PA.

FROM THE SAMUEL D. GROSS SURGICAL DIVISION OF THE JEFFERSON MEDICAL COLLEGE HOSPITAL.

THE SERUM AMYLASE TEST and the trend toward conservative management of acute pancreatitis represent the two recent advances which have widened the recognition of this disease, rendered its diagnosis more certain, and greatly reduced its mortality. Within the past four years 28 cases of acute pancreatitis have been encountered in the Jefferson Medical College Hospital, 20 of the edematous type and eight of the hemorrhagic type. In these, a conservative nonoperative method of treatment¹ was generally employed, reserving operation for the complications, namely, pseudocyst and abscess,² or for associated biliary tract disease. One case from this series is unique in that it followed a nonpenetrating upper abdominal injury. It afforded an unusual opportunity to apply the more recent concepts of diagnosis and treatment to a seldom-recognized and rare type of pancreatitis. Because of the sustained extremely high serum amylase values and the recovery without complications following conservative therapy, we are reporting the case in detail.

Case Report.—D. M., male, age 8, was admitted to the Jefferson Medical College Hospital, September 10, 1945, with the chief complaint of upper abdominal pain.

On September 1, 1945, nine days before admission, the patient fell from a bicycle, striking his upper abdomen on the handle-bars. This was followed by constant moderate upper abdominal pain, not accompanied by nausea or vomiting. On the following day the pain still persisted, accompanied by nausea and one episode of vomiting. He took only liquids and remained in bed all that day and the two succeeding ones. At no time was the pain severe enough to prevent sleep. Except for the first day after the accident the boy's appetite remained good and there were no nausea or vomiting. On the fourth day, because of the persistent mild upper abdominal pain, the family doctor referred the patient to the accident ward with a presumptive diagnosis of appendicitis. Examination at that time revealed a healthy looking boy with normal temperature, pulse and respirations. There was slight tenderness in the right upper and right lower abdominal quadrants and questionable muscle spasticity on this side which could be easily overcome. Rebound tenderness was absent and the rectal examination was negative. The white cell count was 9,000. He was referred to the care of the children's out-patient department.

The following day, the fifth after injury, the boy was free of pain and resumed moderate activity at home. During the ensuing three days the patient remained free of pain, had a good appetite, normal daily bowel movements, and normal color of the urine.

On the morning of the day of admission, nine days after injury, the boy was awakened from sleep by a severe constant periumbilical pain which radiated to both hypochondria. This pain caused him to remain very quiet in bed, doubled up. It was even more severe when he attempted to walk. There was no associated nausea or vomiting. He did not experience shoulder-top or back pain. At no time was blood noted in the stools or urine. Because of the constant severe upper abdominal pain the child was again brought to the hospital.

* Presented before the Atlantic County Medical Society, December 14, 1945.

Physical Examination.—The patient was a well-nourished boy lying with his knees and thighs flexed, complaining of abdominal pain. Temperature 100° F.; pulse 130; respirations 30; and blood pressure 100/70. The face was flushed but not cyanotic. The heart and lungs were normal. On inspection, the abdomen was scaphoid and showed no evidence of external injury. Diaphragmatic excursions were not visible and respirations were entirely thoracic. There were exquisite tenderness, rebound tenderness, and board-like rigidity in the entire upper abdomen and periumbilical area. There was slight muscle-guarding but no tenderness in the lower abdomen. The costovertebral angles were not tender on percussion. There were no visible or palpable abdominal masses. Peristalsis was hypoactive. Rectal examination, as well as the remainder of the physical examination, was negative.

The clinical impression was nonpenetrating upper abdominal trauma with secondary peritonitis.

Laboratory Data.—Examination of the blood showed hemoglobin 71 per cent; red cells 4,200,000; white cells 18,000, with polymorphonuclear cells 90 per cent (10 per cent young forms), eosinophils 1 per cent, lymphocytes 8 per cent, monocytes 1 per cent; and platelets 280,000. Urinalysis was negative. The serum amylase was 320 units (normal 80-180 units). A plain roentgenogram of the abdomen was negative.

Treatment and Progress.—In view of the nine-day interval since injury, the lack of an urgent indication for immediate surgical intervention, and the elevated serum amylase, a policy of watchful waiting was adopted. The vital readings were determined hourly. Slow intravenous administration of 1,000 cc. of 5 per cent glucose in normal saline was instituted. Because of the absence of nausea or ileus, Wangensteen suction was not deemed necessary. Penicillin was administered hypodermically every two hours, the total 24-hour dose being 100,000 Oxford units. During the ensuing 12 hours the pain decreased in intensity, with sedative drugs withheld; the blood pressure remained within normal limits; the pulse fell to 90, the respirations to 22, and the white cell count to 12,000; the abdominal signs became less marked; and a normal bowel movement occurred.

The following day the boy stated that he still had slight pain but was comfortable. There was a further decrease in the severity of the abdominal signs. The hemoglobin and red blood cell count remained essentially the same as on admission and the white cell count fell to 8,000. The serum amylase rose to 400 units. Since intestinal injury appeared unlikely; since signs of intra-abdominal hemorrhage were lacking; and since pancreatic injury, as evidenced by the abnormally high serum amylase, was sufficient to account for the findings, the conservative policy was continued. A record of the serum amylase fluctuations is shown in Chart 1.

During the first week the patient's condition gradually improved. Liquids and soft foods were well tolerated. The pain gradually disappeared altogether and the signs in the right upper abdominal quadrant subsided; but moderate tenderness, rebound tenderness, and rigidity persisted in the left upper quadrant. During the second week the same type of pain as well as the same physical findings noted on admission recurred. There was still no evidence of any upper abdominal mass. On the 10th day after admission the serum amylase reached a peak of 6,400 units, with a corresponding urinary amylase greater than 1,200 units. Repeated white blood cell counts were normal; repeated routine urinalyses were normal; the blood sugar was 66 mg. (14th day of admission); and the serum calcium was 10.1 mg. (15th day). Roentgenologic examination of the upper gastro-intestinal tract with barium on the 16th day of admission showed no evidence of obstruction and no evidence of extrinsic pressure on the stomach.

During the third week the patient again began to improve, and for the ten days prior to discharge on October 10, 1945, he felt well.

Follow-up.—The patient was last reexamined, December 7, 1945, more than three months following the injury. He had remained entirely well following discharge from the hospital. The mother stated that his appetite was excellent and that it was difficult to restrain him from indulging vigorously in sports. Physical examination at this time was

normal. The serum amylase was less than 80 units and blood sugar 80 mg. Roentgenologic study of the upper gastro-intestinal tract with barium was again negative.

DISCUSSION.—Although trauma undoubtedly may cause acute pancreatitis, it is responsible for only a small percentage of cases. In Schmieden and Sebening's³ collected series of 2,137 cases, 62 were of traumatic origin. In Truesdale's⁴ series of 54 cases and in the authors' 28, only one could be directly attributed to trauma. From these figures trauma would seem to account for approximately 2-4 per cent of the cases.

Since the first recorded case of injury to the pancreas by Travers⁵ in 1827, many single case reports have appeared. Most of these injuries, however, have involved other structures as well, such as the spleen, liver, stomach, bowel, kidney, gallbladder, common bile duct, aorta, vena cava, diaphragm, and lung. Thus, Naffziger and McCorkle⁶ encountered associated injury in each of their five cases following nonpenetrating abdominal trauma. There was laceration of the spleen in two, laceration of the spleen and contusion of the kidney in one, laceration of the pylorus and first portion of the duodenum in one, and laceration of the third portion of the duodenum in one. Traumatic pancreatitis without injury to other organs is exceptionally rare. Garre,⁷ in 1905, was able to collect only eight such cases from the literature. Schmieden and Sebening,³ in 1928, found only 20 cases.

Traumatic pancreatitis may follow abdominal injury, either penetrating or nonpenetrating, and also surgical operative injury. The penetrating wounds are most commonly caused by bullets, knives or other pointed objects. Nonpenetrating wounds usually result from blows sustained in falls and fights, or by crushes. The force, whether penetrating or nonpenetrating, is usually anterior, but may be lateral or posterior. Surgical injury may follow operations upon the pancreas itself, as in biopsy or partial pancreatectomy, or on adjacent organs such as the stomach, duodenum, lower end of the common bile duct, or spleen.

Because of its soft parenchymatous and extremely vascular structure the pancreas may be contused or ruptured by what might seem insignificant trauma. Venable⁸ classifies rupture as incomplete or complete. According to this author, incomplete rupture is a tear in the pancreas within an intact capsule. Complete rupture includes a tear in the capsule as well. Either type may or may not be associated with hemorrhage. Severance of the duct of Wirsung may occur, adding greatly to the gravity of the injury, and is usually followed by pancreatic fistula if the patient survives. The pancreatitis that develops may be either the edematous or hemorrhagic type. The hemorrhagic type is apt to be followed by pseudocyst or abscess formation.

As in the usual forms of pancreatitis the symptoms and signs are so variable and so inconstant that it is impossible to make the diagnosis definitely on clinical criteria alone. Any trauma to the upper abdomen should arouse suspicion of this lesion. Definite confirmation can be obtained by the serum amylase test, if the reading is well above the high normal of 180 Somogyi units. During the acute stage of pancreatitis values range from several hun-

dred to several thousand units. In the authors' case the level rose to 6,400 units, which, as far as we are aware, represents the highest value ever reported. It must be borne in mind that symptoms, as well as elevated serum amylase, may follow a latent interval of days or occasionally even weeks. The diagnosis is missed because the condition is not thought of and the serum

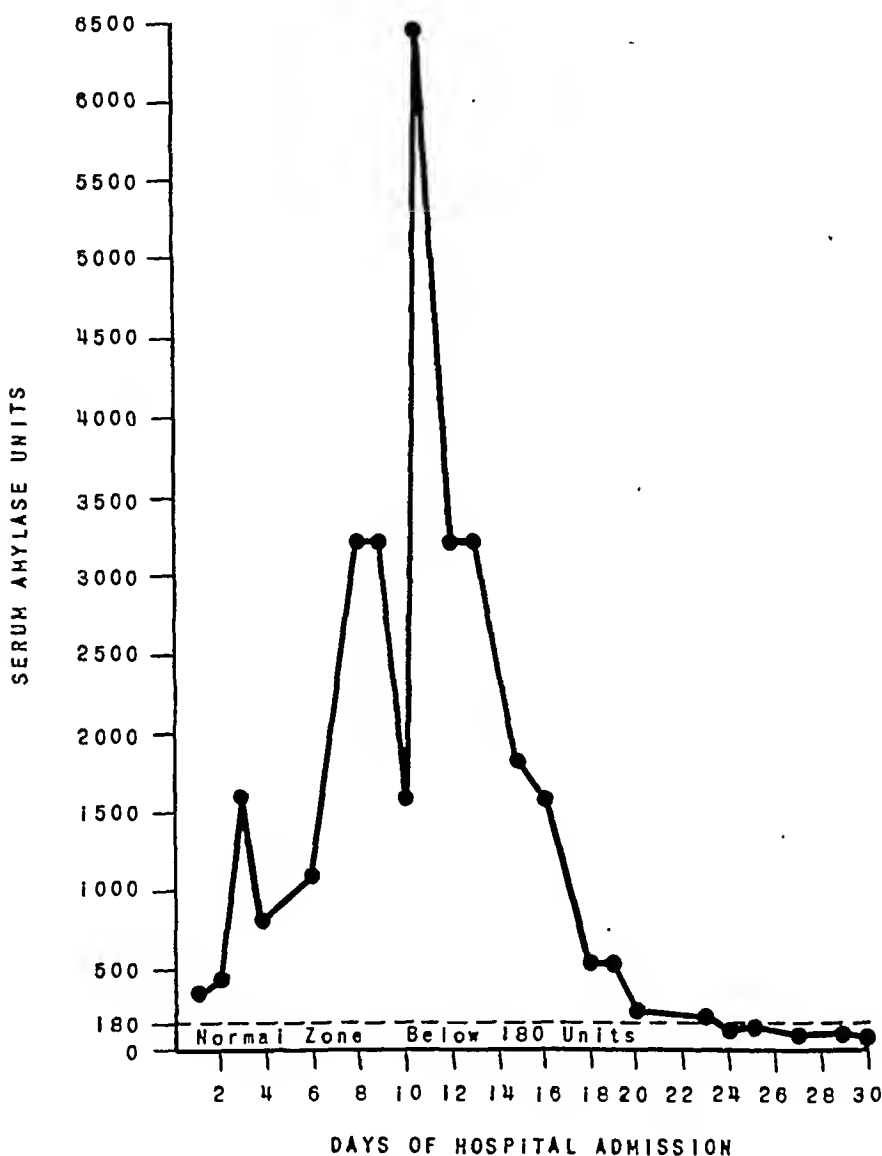


CHART I.—Serum amylase elevations in authors' case, showing sustained extremely high values.

amylase test is not performed. In the authors' case the serum amylase was elevated on the ninth day following injury and remained elevated for three weeks thereafter (Chart I).

According to Naffziger and McCorkle,⁶ in most cases there is a rapid rise and fall of the serum amylase following pancreatic injury, probably corresponding to the period during which enzymes leak from the injured pancreas. Pinkham⁹ believes that a sustained elevation of the serum amylase is suggestive

of the presence of a pancreatic collection. This author urges further clinical observation in such cases in order to derive more data on this point which might aid in the early diagnosis of pancreatic collections. The authors' case in which the serum amylase was sustained at abnormally high levels for three weeks would seem to represent an ideal case for cyst formation, yet this complication did not occur. Obviously the question of the relation of persistent serum amylase elevation to the development of a pancreatic collection can be settled only when many more carefully studied cases are available for analysis.

According to the recent work of Edmondson and Berne,¹⁰ serum calcium findings below 9 mg. per 100 cc. of blood usually occur in cases of pancreatic necrosis some time between the 2d and 15th day of the disease, and values below 7 mg. indicate a fatal prognosis. In the authors' case, on the 15th day of admission, 23 days after injury, the serum calcium was 10.1 mg. at a time when the serum amylase was elevated to 1,600 units. This normal calcium value might be interpreted as indicating pancreatic edema rather than necrosis and certainly was in accord with the favorable outcome of the case.

It is taken for granted that penetrating abdominal wounds associated with pancreatic or other injury should be surgically explored. However, in the treatment of pancreatitis following nonpenetrating abdominal trauma, we believe that the same conservative nonoperative management as recently advocated for the more common forms of pancreatitis is preferable, if injury to important blood vessels and to adjacent organs as the spleen, liver, or gastrointestinal tract can be ruled out. Pancreatic repair is probably greatest when the gland is left undisturbed in a closed abdomen. Since the general reaction and toxemia which may occur result as a rule from primary nonspecific cellular destruction of the pancreas, operation has little to offer. The withholding of food, which acts as a stimulus to pancreatic secretion; Wangensteen suction to combat ileus; oxygen in severe cases; and intravenous administration of saline solution, glucose, amino-acids and vitamins support the patient during the vital period in which the complication of pancreatic collection either infected or noninfected may occur. Chemotherapy in the form of penicillin is a valuable adjunct in preventing secondary bacterial invasion.

If clinical improvement occurs within a few hours and persists, as in the authors' case, it is justifiable to continue a conservative policy of treatment. On the other hand, if the patient's condition becomes progressively worse during the ensuing 4-12 hours, surgical intervention is indicated, for further delay may prove disastrous. Lacerations following stab wounds and tearing injuries may be closed with black silk, but the contused lacerations following nonpenetrating injuries usually cannot be closed. In these instances Penrose drains should be placed in the lesser peritoneal cavity adjacent to the capsule of the injured pancreas and brought to the surface, either through the original incision or a separate one in the flank. The purpose of the drainage is to aid in prevention of diffuse peritonitis or formation of a pancreatic collection (hematoma, abscess, or pseudocyst).

Pseudocyst formation may occur weeks or months subsequent to the original injury. Pinkham⁹ who reviewed recent series of pancreatic pseudocysts states that trauma is responsible for 20 per cent, or less, of the cases. Treatment of these is surgical, consisting of marsupialization of the cyst. Although the authors' case shows no evidence of this complication after three months, continued follow-up study is indicated to exclude it as a very late manifestation of traumatic pancreatitis.

SUMMARY AND CONCLUSIONS

1. Trauma accounts for approximately 2-4 per cent of cases of acute pancreatitis. Following an upper abdominal injury, acute pancreatitis should always be suspected. A latent period may intervene before appearance of symptoms.

2. Suspicion of traumatic pancreatitis should be confirmed by performance of the serum amylase test, the reliability of which, during the acute phase of pancreatitis, has become firmly established.

3. Operation is not necessary in all cases of pancreatitis following injury. The conservative nonoperative management which has greatly reduced the mortality in the usual types of pancreatitis is advocated for cases following nonpenetrating abdominal injury, if serious injury to other organs and massive hemorrhage can be ruled out.

4. Indications for surgical intervention are penetrating wounds; injury to important blood vessels; injury to adjacent viscera as spleen, liver or gastro-intestinal tract; failure to respond promptly to conservative management; or for subsequent pancreatic collections.

5. A case is presented and discussed in which the diagnosis was suspected clinically, confirmed by the serum amylase test, treated conservatively, and in which recovery ensued without complications.

REFERENCES

- ¹ Shallow, T. A., Eger, S. A., and Wagner, F. B.: The Conservative Management of Acute Pancreatitis. *Pennsylvania Med. Jour.*, 47, 1199, 1944.
- ² Shallow, T. A., Eger, S. A., and Wagner, F. B.: Suppurative Pancreatitis with Associated Liver Abscess. *ANNALS OF SURGERY*, 121, 853, 1945.
- ³ Schmieden and Sebening, W.: Surgery of the Pancreas. *Surg., Gynec. and Obst.*, 46, 735, 1928.
- ⁴ Truesdale, P. E.: Acute Pancreatitis: A Review of Fifty-four Operative Cases. *New Eng. Jour. Med.*, 210, 66, 1934.
- ⁵ Travers, B.: *Lancet*, 12, 384, 1827.
- ⁶ Naffziger, H. C., and McCorkle, H. J.: The Recognition and Management of Acute Trauma to the Pancreas: With Particular Reference to the Use of the Serum Amylase Test. *ANNALS OF SURGERY*, 118, 594, 1943.
- ⁷ Garre: Totalen Querriss des Pankreas durch Naht geheilt. *Beitr. z. klin. Chir.*, 46, 233, 1905.
- ⁸ Venable, C. S.: Rupture of the Pancreas. *Surg., Gynec. and Obst.*, 55, 652, 1932.
- ⁹ Pinkham, R. D.: Pancreatic Collections (Pseudocysts) Following Pancreatitis and Pancreatic Necrosis. *Surg., Gynec. and Obst.*, 80, 225, 1945.
- ¹⁰ Edmondson, H. A., and Bernc, C. J.: Calcium Changes in Acute Pancreatic Necrosis. *Surg., Gynec. and Obst.*, 79, 240, 1944.

THE SURGICAL TREATMENT OF 1,545 HERNIAE

FRANK GLENN, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY OF THE NEW YORK HOSPITAL AND
CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N. Y.

IN 1936 a report¹ was made from this clinic on experiences with 500 herniae treated by surgery. This paper presents an account over a five-year period, from 1940 through 1944, inclusive, of 1,545 herniae subjected to operation. The results have been good when early surgical treatment has been initiated. There have been recurrences as well as postoperative complications. This review is undertaken in order to evaluate the procedures employed and to consider what changes in present methods are indicated. The analysis of 1,545 herniae performed covers 1,385 consecutive patients, of whom 770 had indirect inguinal, 205, direct inguinal, 95, recurrent inguinal, 110, femoral, 57, umbilical, 12, epigastric and 136, postoperative ventral herniae. In this series there were 95 postoperative complications and six deaths. There has been a continuous effort to keep the incidence of infection and postoperative pulmonary complications at a minimum, two factors which contribute to recurrences. The deaths in this group were due to complications of the vascular system or infection resulting from delayed intervention.

General Technic.—The careful evaluation of every patient with hernia is essential to secure the least possible incidence of postoperative complications which are few in the young adult, but in the extreme age-groups are frequent. Infants with acute herniae require special attention as to fluid balance, and elderly patients, males in particular, require investigation of the lower urinary tract for partial obstruction that may be an etiologic factor in the development of the hernia or in its recurrence after operation. Direct hernia often develops as the result of repeated straining in initiating or maintaining micturition. The large postoperative ventral herniae that contain a fair portion of the abdominal contents are always a problem in preoperative preparation. They require the return of the hernial contents to the abdomen prior to operation by various means including rest in bed for periods up to a week so that the respiratory system will not be embarrassed after operation. Preoperative decompression of the gastro-intestinal tract with catharsis, and postoperative decompression by means of a Miller-Abbott tube or Wangensteen suction have contributed toward keeping distressing and sometimes serious abdominal distention at a minimum.

Anesthesia.—Local anesthesia was employed in over two-thirds of all herniae repaired. Postoperative complications were as frequent in the group in which local anesthesia was used as in that in which general anesthesia was used. However, local anesthesia was employed in almost all patients of the older age-group, and it is in this group that the incidence of pulmonary com-

plications is highest. Retching and vomiting, not uncommon after general anesthesia, do place an extra strain on the freshly repaired hernia.

Local anesthesia.....	1,090
General anesthesia.....	397
Local and general.....	37
Spinal anesthesia.....	21

Suture Material.—Silk suture material was used in all repairs except 19 in which catgut, and eight in which cotton was employed. It may be said that catgut was limited to the repair of acute herniae in which infection was believed to be present. Cotton has more frequently been used since 1944 and is becoming increasingly popular. There are reports in the current literature that indicate that cotton suture material has many advantages.

Postoperative Care.—For the most part, patients operated upon for hernia have been kept in bed for a period of wound healing of 14 days and more. However, the recent trend has been to mobilize patients who possess good anatomic structures, as, for example, the young adult male with a congenital type of indirect inguinal hernia. We think that such patients may be ambulant after operation without much likelihood of recurrence. In those patients whose defects are large or whose structures involved in the repair are of poor quality we maintain that a full period of wound healing is required before any unnecessary strain be placed upon the repair. Likewise, greater attention has been given the protein intake of all patients to correct any deficit in nitrogen balance.

Inguinal Hernia.—In a total of 1,070 patients, 1,222 inguinal herniae were repaired. Of these 840 were indirect, 279 were direct and 103 were recurrent.

Indirect Inguinal Hernia.—In the majority of instances on this Surgical Service we continue to repair the indirect inguinal hernia in one of two ways. If the structures are good quality and the defect small, a simple anatomic repair without transplantation of the cord is done. As described by Halsted, the sac is dissected up to its neck where it is ligated and transfixed with double medium silk. The stump retracts behind the internal oblique muscle. The cremaster muscle and fascia are drawn up under the edge of the conjoined tendon and the internal oblique muscle in an effort to partially obliterate the inguinal canal. The internal oblique muscle and conjoined tendon are then sutured to Poupart's ligament with interrupted sutures of medium silk so that they closely embrace the cord as it emerges. The margin of the lateral portion of the external oblique is then secured beneath the mesial portion by a series of mattress sutures. The mesial portion of the external oblique is brought to overlap this laterally and secured in a similar manner. Interrupted black silk sutures are employed throughout the procedure.

If the structures are weak or if the defect is large, a Halsted repair with transplantation of the cord to the subcutaneous tissue is done. We have come to use this method more frequently if structures are not good. Discomfort from a cord transplanted to the subcutaneous tissue has been rarely observed. In this procedure all muscular and fascial layers are united beneath the cord, with

the complete obliteration of the old external ring. The new external ring, although nearly opposite the internal ring, is believed to permit recurrence less frequently.

The Bassini operation has enthusiastic advocates among some of the surgeons of the clinic but has not proved as satisfactory as the Halsted operation with transplantation of the cord to the subcutaneous tissue.

In the 840 inguinal herniae the repairs were as follows:

Simple anatomic repair.....	610
Halsted transplant of cord.....	188
Bassini transplant of cord.....	22
Torek procedure, simple repair.....	20

Silk suture material was used in 825, catgut in 8, and cotton in 7 instances. The operation was performed under local anesthesia in 606, general in 216, local supplemented with general in 10, and under spinal anesthesia in 8.

There were three deaths, one following coronary occlusion, one the result of a pulmonary embolus, and the third occurring in a six-weeks-old infant who had peritonitis at the time of operation. The mortality rate for this group was 0.35 per cent.

The other postoperative complications were 49 in number, an incidence of 5.8 per cent.

Urinary retention.....	11
Wound infection.....	9
Atelectasis.....	8
Pulmonary infarct.....	4
Pneumonia.....	4
Coronary occlusion.....	2
Fecal fistula.....	2
Cystitis.....	2
Swollen testicle.....	2
Phlebitis.....	1
Miscellaneous.....	4

49

Follow-up.—Five hundred and fifty-nine of the 770 patients operated upon for indirect inguinal hernia were examined in the follow-up clinic. Six hundred and sixteen hernia repairs were examined revealing 19 recurrences, an incidence of 3.0 per cent.

Direct Inguinal Hernia.—The direct inguinal hernia is seen in the older age-group as the result of an acquired attenuation of the structures which comprise the conjoint tendon. The part played in the development of these herniae by the repeated increase in intra-abdominal pressure during urination and defecation because of obstruction of the bladder outlet or large bowel is now well recognized; and an examination of the lower gastro-intestinal tract and urinary tract should be made before operation on the hernia is undertaken. Two hundred and five patients were operated upon and 279 herniae repaired.

Although these patients were in the older age-group, there were no post-

operative deaths and only 19 instances of postoperative complications, an incidence of 6.7 per cent. These were:

Wound infection.....	6
Atelectasis.....	3
Swollen testicle.....	3
Hematoma.....	2
Phlebitis.....	2
Pulmonary infarct.....	1
Coronary occlusion.....	1
Influenza.....	1

The type of repair employed was:

Halsted transplantation of cord.....	224
Simple anatomic repair.....	33
Bassini transplantation of cord.....	22
	<hr/>
	279

Silk was used as suture material in all except two cases, one which was repaired with cotton, the other with catgut.

The operation was done under local anesthesia in 245 instances, local and general in 3, general in 28, and spinal in 3.

Two hundred and twenty herniae repairs were inspected on follow-up examination. There were 18 recurrences, an incidence of 8.1 per cent.

Recurrent Inguinal Hernia.—There were 95 patients who had 103 recurrent inguinal herniae. Twelve of these herniae were of the indirect type and the remainder (91) were direct. The type of repair employed was with few exceptions that of Halsted, with transplantation of the cord to the subcutaneous tissue.

Halsted transplantation of cord.....	88
Bassini transplantation of cord.....	8
MacFee ² hernioplasty.....	2
Anatomic repair.....	5

All repairs were with silk suture material except one in which catgut was used. Anesthesia employed was local in 93, general in 7, local and general in 1, and spinal in 2.

There were no deaths following operation, but six instances of complications, an incidence of 5.8 per cent.

Wound infection.....	2
Pulmonary infarct.....	1
Atelectasis.....	1
Bronchopneumonia.....	1
Swollen testicle.....	1

Eighty-six patients were examined in the follow-up clinic and 95 herniae inspected of which 14 had recurred, an incidence of 14.7 per cent.

Femoral Hernia.—There were 110 patients with femoral hernia in four of whom the condition was bilateral, making a total of 114 herniae. There were 90 women and 20 men in this group. Ninety-three of these patients were over 40 years of age and 53 were over 50. Eighteen patients were admitted to the hospital with acute strangulation of the bowel, which was demonstrated at operation.

The operative procedure was done under local anesthesia in 91, local and general in 3, general in 17 and spinal in 3 cases. Silk was used exclusively for the repair when the operation consisted of the simple anatomic closure of the defect with approximation of the pectineus fascia to Poupart's ligament. In 30 cases a variety of procedures were employed including transperitoneal approach above the inguinal ligament and the method recently described by Moore.³

There was one death from peritonitis which was present at the time of operation for acute strangulation of small bowel, a mortality rate of 0.87 per cent. There were seven postoperative complications, an incident of 6.1 per cent which is fairly low considering the age-group.

Phlebitis.....	2
Peritonitis.....	2
Wound infection.....	2
Pulmonary infarct.....	1

Ninety-four hernia sites were examined in the follow-up clinic and eight recurrences found, a recurrence rate of 8.5 per cent.

Umbilical Hernia.—Six of 57 patients with umbilical hernia had previously been subjected to operation for this condition. Thirty-one of this group were over 40 years of age and only two were under 18. There were 38 females and 19 males. Fifty-five herniae were repaired with silk and two with catgut. Local anesthesia was used in 35 patients and general in 22. Eight of the herniae were acute on admission to the hospital. Twenty-two were simple anatomic repairs, 19 were operated upon according to the Mayo⁵ method and 16 according to the Blake⁴ method.

Forty-three patients were examined in the follow-up clinic and five recurrences demonstrated, an incidence of 11.8 per cent.

Epigastric Hernia.—Only 12 patients were operated upon for epigastric hernia. These were all located in the midline above the umbilicus and were considered the cause of epigastric pain. Five were multiple, the remainder single. None had been operated upon before. A simple anatomic repair was done with silk in 11 and a modification of a Blake procedure with overlapping of the fascia in one case. Complete relief of epigastric pain was obtained in nine of the 11 patients. There were no deaths and no complications.

Eleven of these patients were reexamined in the follow-up clinic and one recurrence observed, an incidence of 9 per cent.

Postoperative Ventral Hernia.—The 136 patients with ventral herniae presented all types varying from small defects following drained appendicectomy wounds to large herniae which contained much of the abdominal contents. Seven were recurrent ventral herniae. Sixteen patients were admitted to the hospital because of acute intestinal obstruction due to strangulation of the bowel. This group may be said to present more difficult surgical problems than all the others in this study since it includes the debilitated, the obese and those who, following previous operations, have had severe and extensive wound infections.

One hundred and forty-five postoperative ventral herniae in the group of 136 patients were repaired. There were two deaths (mortality 1.4 per cent); one resulted from a pulmonary embolus, the other from peritonitis following operation for an acute hernia. Twelve complications were as follows:

Wound infection.....	4
Atelectasis.....	2
Fecal fistula.....	2
Coronary occlusion.....	1
Pulmonary embolus.....	1
Hematoma of wound.....	1
Peritonitis.....	1

One hundred of these patients were reëxamined in the follow-up clinic. There were 12 recurrences, an incidence of 12 per cent.

Postoperative Complications.—In the group of 1,385 consecutive patients with 1,545 herniae, 95 patients developed postoperative complications varying in significance, six of which ended in death. There were 13 instances of atelectasis, five of pneumonia and eight of pulmonary infarction. Phlebitis of the lower extremities was noted only 15 times. Coronary occlusion occurred twice and was fatal in one instance. The operative wound was infected in 22 patients, the majority of infections following operation for acute herniae. Seven patients developed peritonitis following operation for intestinal obstruction, a late complication of hernia. In this group fecal fistula was established or developed in four instances. Hematoma requiring revision of the wound occurred in three patients, and swollen testicle in six. Urinary retention, which required an indwelling catheter followed operation for hernia in 11 patients, and a serious cystitis developed or recurred in two women during the postoperative period in the hospital. There were seven miscellaneous complications, such as influenza, measles, otitis media, acute psychosis, etc. The cause of death in six patients was:

Peritonitis.....	3
Pulmonary embolus.....	2
Coronary occlusion.....	1

Follow-up.—The late results presented in this paper are based upon observations made in the surgical follow-up clinic six months to three years, or longer, after the patients were discharged from the hospital.

Patients operated upon for hernia are followed at six-month intervals up to three years. About 75 per cent, or 1,037 of the 1,385 patients who compose this group, were examined after operation by a surgeon other than the operator. The incidence of recurrence among the recurrent inguinal herniae as reported by clinics with adequate follow-up facilities ranges from 10 to 30 per cent. Those,⁶ using Gallie's method of fascial suture, have not reported better results than those employing silk or cotton. The use of fascial sutures for the repair of inguinal hernia has for the most part been abandoned. The

method advocated by MacFee,² in which the cord is transplanted to the femoral canal, offers promise.

Acute Hernia.—This term has been employed to designate those patients who require immediate operation because of incarceration or strangulation of bowel. An incarcerated hernia may not necessarily be an emergency but immediate operation to exclude the possibility of strangulation is often indicated because the transition from incarceration to strangulation and intestinal obstruction occurs too frequently to be disregarded.

The recent^{7, 8} literature reveals that silk is today employed most frequently in the repair of hernia. Cotton suture material is becoming more popular and the use of fine steel wire, as advocated by Babcock, is increasing. As more reports on the experience of early mobilization of patients after operation appear, it is evident that the trend to get patients with repair of indirect inguinal hernia of the congenital type out of bed on the day following operation is justified. However, until longer follow-up studies are available, definite conclusions cannot be stated. The mobilization of the structures in the repair of any hernia and their meticulous approximation without tension by suture material that produces the least reaction, as insisted upon by Halsted⁹ in 1893, remains the important principle in this field of surgery.

TABLE I
SUMMARY OF RESULTS IN 1545 HERNIA OPERATIONS

Type of Hernia	Number of Patients	Number of Operations	Total Patients Followed	Follow-up Results		
				Number of Hernia Repairs Examined	Number of Recurrences	Percentage of Recurrences
Indirect inguinal.....	770	840	559	616	19	3.0
Direct inguinal.....	205	279	144	220	18	8.1
Recurrent inguinal.....	95	103	86	95	14	14.7
Femoral.....	110	114	94	94	8	8.5
Umbilical.....	57	57	43	43	5	11.8
Epigastric.....	12	12	11	11	1	9.0
Postoperative ventral.....	136	140	100	100	12	12.0

CONCLUSIONS

1. Fifteen hundred and forty-five herniae treated surgically over a five-year period (1940-1944) are reported.
2. The majority of the postoperative complications are systemic and are of vascular or pulmonary origin. Local complications for the most part are due to infection.
3. Fifty per cent of the deaths and many of the complications occurred in patients who presented themselves for operation with "acute" hernia.

REFERENCES

- ¹ Glenn, Frank, and McBride, A. F.: The Surgical Treatment of Five Hundred Herniae. ANNALS OF SURGERY, 104, 1024-1029, 1936.

- ² MacFee, W. F.: Repair of Inguinal Hernia with Transplantation of Cord to Femoral Canal. *Tr. Am. S. A.*, 58, 637, 1940.
- ³ Moore, S. W.: Femoral Hernia. *Surgery*, 13, 45-151, January, 1943.
- ⁴ Blake, J. A.: The Operative Treatment of Umbilical Hernia in Adults. *Med. Rec.*, 59, 803, 1901.
- ⁵ Mayo, W. J.: Further Experience with the Vertical Overlapping Operation for the Radical Cure of Umbilical Hernia. *J. A. M. A.*, 41, 225, 1903.
- ⁶ Burdick, C. G., and Gillespie, H. M.: Fascial Suture Operations for Herniae; End-results of 1485 Cases. *ANNALS OF SURGERY*, 106, 333, 1937.
- ⁷ Erdman, S.: Hernia. *Surgery—Text Book*, Christopher, W. B. Saunders, Philadelphia and London, 1945.
- ⁸ Maier, R. L.: Results of Silk Technic in Operations for Hernia. *ANNALS OF SURGERY*, 113, 312-314, 1941.
- ⁹ Halsted, W. S.: The Radical Cure of Inguinal Hernia in the Male. *Johns Hopkins Bull.*, 4, 17, 1893.

SCALENOTOMY

AN ANALYSIS OF ELEVEN CASES DONE FOR SCALENUS ANTICUS SYNDROME

JEROME F. TANNA, M.D.

NEW ORLEANS, LA.

FROM THE NEW ORLEANS CHARITY HOSPITAL, NEW ORLEANS, LA.

THE SCALENUS ANTICUS SYNDROME is a term applied to a definite clinical entity that has come into prominence during the last ten to 12 years.

Probably the first reference to the scalenus anticus syndrome was made by John B. Murphy¹ in 1906, who called attention to the rôle of the scalenus anticus in the production of symptoms in patients who also had a cervical rib. Adson and Coffey,² in 1927, advocated section of the scalene muscle instead of the removal of the cervical rib in cases where the cervical rib was present, and claimed that it was unnecessary to remove the rib in most cases. In 1935, Ochsner, Gage and DeBakey³ published a comprehensive study of the subject to which they gave the name "Scalenus Anticus Syndrome," advancing the latter as a definite clinical entity, the symptoms of which are identical with those of cervical rib. They credit Naffziger with being the first to section the scalenus anticus muscle for the relief of symptoms in the absence of a cervical rib. Since 1935, several authors have reported *bona fide* cases of scalenus anticus syndrome which have been benefited by section of the scalenus anticus muscle.

Etiology.—A variety of causes for the production of this syndrome have been offered. Adson² believed that the symptoms were attributable to two factors: the muscular development of the young adult whose bulging scalene muscles produced the symptoms; and, in older persons, relaxation of the musculature with sagging of the shoulder girdle producing the symptoms. Gage⁴ contends that there exists a definite vicious circle that is responsible for the production of symptoms in this clinical entity. This consists of spasm of the scalenus anticus muscle (probably from trauma), which, in turn, elevates the first rib and compresses the brachial plexus, which increases the spasm of the scalenus anticus by reflex action. Todd⁵ attributed the predisposition of this symptom complex to faulty development. Normally, during developmental years, the acromial end of the clavicle and the shoulder descend because of the weight of the upper extremity; and the sternal end of the clavicle descends because of contracture of the rectus abdominis muscle which is exerted through the sternum. Either, or both, of a greater than normal descent of the shoulder girdle and a lack of descent of the sternal end of the clavicle may result in compression of the subclavian structures in the scalene angle formed by the first rib and scalenus anticus muscle.

Jones⁶ attributes the syndrome to abnormal development of the brachial plexus. In those cases in which the brachial plexus is derived mainly from the cervical segments of the spinal cord, no symptoms occur; whereas, in those

cases in which a considerable portion of the brachial plexus is derived from the thoracic segments, symptoms are likely to develop.

Gage's traumatic vicious circle conception seems to enjoy the greatest popularity.

Haven⁷ pointed out that the neurocirculatory symptoms found in the scalenus anticus syndrome may be due to an anomalous formation of the first rib. Roentgenograms in some of his cases revealed an enlarged and short rib which, instead of continuing around to the sternum, formed a synostosis with the second rib at its termination about one-third of reaching the sternum. Relief in these cases was afforded by scalenotomy. Pommerenke and Risteen⁸ report four cases of scalenus anticus syndrome as a result of injury to the scalenus anticus muscle due to faulty position of the patient on the operating table. The patient in the Trendelenburg position with the head extended and the arm abducted with the shoulder jammed against braces may sustain injury sufficient to cause symptoms. In two of their cases it was necessary to section the scalene muscle to obtain relief. D'Abreu⁹ cites the following: In a tuberculous patient with a fully-formed left cervical rib and an enlarged costal element of the right seventh cervical transverse process to which was attached a fibrous cord, the symptoms of right cervical rib syndrome developed after the upper part of the chest on that side had contracted down during the healing process.

Clinical Picture.—The symptoms of scalenus anticus syndrome may be divided into two types: neurologic and vascular.

The neurologic manifestation may originate from both the somatic nervous system and the sympathetic nervous system. Pain may be experienced in the shoulder, arm, forearm, or even extending into the hand. The pain sometimes extends to the cervical spine, to the scapula, and to the thoracic wall. Two of the cases reported in this paper first noticed pain in the breast of the involved side. The character of the pain is variable; it may be of the acute, lancinating type or dull or aching. In some instances the patient experiences remissions and exacerbations alternately. Characteristically, the pain is brought on or aggravated by continuous use of the arm or after repeated movements, such as rotation or extension of the neck. The act of sweeping notoriously causes aggravation of the pain.

Pain can be produced by making pressure over the scalenus anticus muscle; and Gage¹ demonstrated that the pain could be completely relieved by injecting the anterior scalene muscle with one per cent novocaine, which causes a relaxation of the muscle. These patients will seek relief by attempting to keep the shoulder elevated, such as carrying the arm in a sling.

Pressure on the somatic nerves in the scalene angle may produce atrophy of the muscles supplied, most usually of the intrinsic muscles of the hand because the ulnar nerve is most frequently involved. Fibrillary muscular twitching may also be noted.

Sympathetic nervous involvement is manifested by vasomotor spasm, lack of capillary action in the fingers, and reduction of temperature which frequently simulates Raynaud's disease.

Vascular compression is manifested by an obliteration or partial reduction of the pulse volume when the head is turned toward the side of the lesion and a deep inspiration is taken. The blood pressure may be reduced and the pulse may be diminished or absent on the involved side. Ischemia with resultant atrophy may be present. MacFee¹⁰ reports a case in which there was the formation of an aneurysm of the third portion of the subclavian artery distal to the point of constriction, with gangrene of the finger tips. It is noteworthy that nearly all dilatations of the subclavian artery have been distal to the point of constriction. There is no completely satisfactory explanation why the dilatation should occur at this point. Suggestions which have been offered are: Slowing of the blood stream with a resulting increase of lateral pressure; limitation of blood supply to the vessel wall through interference with the vasa vasorum; and trophic changes in the vascular structure due to paralysis of the sympathetic nerve supply. McLaughlin and Popma¹¹ reported a case of intermittent obstruction of the subclavian vein due to spasm of the anterior scalene muscle. The patient suffered with intermittent swelling and cyanosis of the entire right upper extremity following exertion. Judovich, Bates and Drayton¹² found that compression of the subclavian vein may be caused by spasm of the scalenus anticus causing narrowing of the costoclavicular space or perhaps by pressure on an anomalous subclavian vein passing behind the scalene muscle.

Other findings are inability to elevate the arm above the head, fibrillary twitchings of the various muscles of the upper extremity, fullness of the supraclavicular space, and elevation of the shoulder on the affected side.

Early vascular changes may be elicited by means of the Tycos recording sphygmomanometer. By this method diminished pulse volume may be determined on the involved side.

Differential Diagnosis.—Scalenus anticus syndrome is not difficult of diagnosis if the condition is kept in mind. Conditions from which it must be differentiated are: cervical rib, cervicodorsal sympathalgia, Raynaud's disease; subacromial bursitis; supraspinatus tendon rupture; and brachial neuritis. The clinical picture produced by cervical rib is identical with that of scalenus anticus syndrome, their mechanism of production being the same. Occasionally, cervical ribs produce more marked symptoms. Cervical rib can be definitely ruled out by roentgenography. Cervicodorsal sympathalgia may very closely simulate scalenus anticus syndrome because of the nervous and vascular phenomena common to both. The former condition can be definitely eliminated by the complete relief of symptoms following novocaine block of the cervicodorsal sympathetic ganglia. Raynaud's disease is usually bilateral; whereas scalenus anticus syndrome is usually unilateral. The somatic nervous manifestations in Raynaud's disease are absent. In subacromial bursitis and supraspinatus tendon rupture, the tenderness is limited over the supraspinatus tendon and subacromial bursa without other accompanying nervous and vascular manifestations. Atrophy of the deltoid may be a prominent symptom. Abduction of the arm usually increases the pain in cases with subacromial bursitis; whereas this position brings relief in cases of scalenus anticus syndrome. Further, roent-

genograms frequently show calcification in the region of the tendon and bursa. Brachial neuritis must be considered if local infiltration of 1 per cent novocaine into the scalenus anticus does not bring relief of symptoms.

Treatment.—Ochsner³ feels that conservative methods offer relatively little; and that the only method by which one may obtain complete and permanent relief is by performing scalenotomy. He is of the opinion that the beneficial results by scalenotomy are due to the break in the vicious circle which allows the first rib to assume a lower position, thus, relieving the pressure both on the subclavian artery and the brachial plexus. This is based on the operative observation of the sudden depression and disappearance into the depths of the wound of the first rib following division of the anterior scalene muscle. It is advised that it is desirable not only to divide but also to resect the distal portion of the scalenus anticus muscle because of the possibility of fibrous bridging between the two ends of the divided muscle resulting from organization of exudates.

Hansson¹³ observes that several surgeons with extensive experience in the handling of symptoms produced by cervical rib or spasm of the scalenus anticus muscle are agreed that surgical intervention is necessary in only 15 to 20 per cent of the cases. The remainder can be handled by conservative treatment of rest and support, heat to relieve pain and spasm, massage to increase muscular tone and exercise to build up muscular support. He states that postural correction of body mechanics is important and even those who come to surgery should have the benefit of conservative management as a complementary measure. Reichert¹⁴ reports that the majority of patients suffering with this syndrome can be relieved by correcting waking and sleeping posture. Smith¹⁵ presents a case of scalenus anticus syndrome with symptoms simulating coronary disease, without a cervical rib; but with the thickened lateral edge of the cervical fascia posterior and lateral to the scalenus anticus muscle pressing on the third portion of the subclavian artery, resulting in a thrombosis which had become an organized fibrous cord. Division of the fascia where it compressed the artery relieved all of his cardiac symptoms, the pain in his shoulder and arm, and the intermittent claudication while at work as a soda dispenser. He states that there was no evidence, at operation, of compression of the nerves of the brachial trunk.

Patterson¹⁶ believes that, when a cervical rib is present in conjunction with the scalenus anticus syndrome, it is necessary to divide both the anterior and medial scalene muscles and also to resect the cervical rib in order to effect a cure.

In the past, there has been some tendency to include too many disturbances of the upper extremities under the term of "scalenus anticus syndrome," and also a tendency to perform scalenotomy without first determining the exact nature of the symptom complex. For instance, Nachlas¹⁷ doubts that spasm of the anterior scalene muscle is responsible for the production of symptoms. He contends that the scalene angle is actually increased instead of decreased by spasm of the muscle. He further points out that many patients who have

come under his care after having had scalenotomy have shown no improvement. It is his contention that this symptom complex is not primarily caused by spasm of the scalenus anticus, but that the symptoms are associated with lesions of the cervical spine that produce intervertebral foraminal compression of the nerve roots. Falconer¹⁸ describes three cases in which compression of the subclavian vessels with obliteration of the radial pulse was due to compression of the vessels between the clavicle and the first rib. At the time of operation, it was shown that, after section of the muscle, hyperextension of the neck still caused obliteration of the radial pulse, showing that spasm of the scalenus anticus was not the primary factor. Procaine was injected into the muscle to differentiate this mechanism for the production of symptoms from the true scalenus anticus syndrome. The treatment in these cases, with good results, was removal of a portion of the rib and its periosteum to relieve the compression. Semmes and Murphey¹⁹ record that an undetermined number of patients who, heretofore, have been thought to have coronary occlusion, angina pectoris, hypertrophic arthritis of the cervical spine, neuritis of the brachial plexus, bursitis, scalenus anticus syndrome or cervical rib, have, in reality, been suffering with ruptured intervertebral disk of one of the lower cervical vertebrae. Aitken and Lincoln²⁰ report a case of fractured first rib, a rare condition, which presented all of the symptoms of scalenus anticus syndrome. Relief was obtained by immobilization of the head and neck. Freiberg²¹ points out that spasm of the scalenus anticus may be secondary to cervical arthritis or lesions of the shoulder girdle, and that correction of these primary lesions is all that is necessary. Brown²² reports a case of "winged scapula" as a result of paralysis of the trapezius muscle which followed injury to the spinal accessory nerve. The paralysis of the trapezius caused sufficient sag of the shoulder girdle to place the scalenus on stretch with resultant hypertrophy and spasm, thus, producing the neurocirculatory symptom-complex. Repair of the injury effected a cure. Bishop²³ has shown that calcification of the supraspinatus tendon as a result of repeated minor injuries may cause the scalenus anticus syndrome, the *modus operandi* being reflex spasm of the scalenus anticus muscle.

There are reviewed in this communication 11 consecutive cases of scalenus anticus syndrome for which scalenotomy was done, during the period 1939-1945, at the New Orleans Charity Hospital (Table I).

Incidence.—The age-incidence in the 11 cases ranged from 18 to 57 years, with an average of 34 years. The majority occurred in the third decade, which showed four cases. There were nine female and two male patients, of which two were colored females. The left side was involved in seven cases and the right side in four. A relationship between the onset of symptoms and preceding excessive or unusual use of one of the upper extremities was shown in two cases. In one case, the patient became symptomatic after indulging in heavy work; in the other, the patient noticed symptoms after suddenly lifting a baby. The occupations of the others were varied and irrelevant.

Symptoms.—The duration of symptoms varied from three weeks to several years with eight of the 11 cases being three months or less. The symptoms

TABLE I
ANALYSIS OF ELEVEN CASES OF SCALENUS ANTICUS SYNDROME

Case No.	Age	Sex	Side Involved	Duration of Symptoms	Total or		Muscular Weakness	Muscular Atrophy	Pulse	B.P. Diff.	Reflex Changes	Roentgen Findings	Ray Operation	Result of Operation	Time of Relief
					Pain	Partial Disability									
1	57	M	Rt.	4 wks.	++	P	Slight	O	O	Strong	Same	?	Scalenotomy	Excellent	Immed.
2	22	F	Left	2 mos.	++++	P	O	O	O	?	?	Unilateral cervical rib	Scal. & removal of rib	Excellent	Immed.
3	32	F	Left	2 mos.	++	P	O	O	O	?	Increased	Neg.	Scalenotomy	Excellent	Immed.
4	28	F	Left	2 mos.	+	O	Slight	Slight	O	Same	Elev.	Bilateral cervical ribs	Scal. & removal of rib	Poor	
5	41	M	Left	3 mos.	++	O	Slight	O	O	?	?	Neg.	Scalenotomy	Excellent	Immed.
6	25	F	Left	2 mos.	+	O	O	O	O	Weak	Elev.	?	Scalenotomy	Excellent	Immed.
7	18	F	Left	3 mos.	++	O	O	O	O	?	?	?	Scalenotomy	Excellent	Immed.
8	41	F	Rt.	3 wks.	++	O	O	O	O	Weak	Same	?	Scalenotomy	Excellent	Immed.
9	23	F	Rt.	4 yrs.	+	O	O	O	O	?	Same	?	Unilateral cervical rib	Good	Immed.
10	34	F	Rt.	Several years	+	O	Slight	O	O	O	Same	?	Scalenotomy	Excellent	Immed.
11	54	F	Left	7 mos.	++	P	Slight	Slight	O	?	?	Neg.	Scalenotomy	Excellent	Immed.

were variable; and, except for the more prominent objective signs in those cases having cervical ribs, were, in general, essentially the same. The most consistent symptom was pain ranging from the dull, aching type to the sharp, lancinating type. Numbness was recorded in five cases and muscular weakness in two cases. No cases were recorded as having muscular atrophy. In the majority of cases, the location of pain was the side of the neck, shoulder, and upper arm. Two of the female patients first noticed pain over the breast on the involved side.

Reflex Changes.—Reflex changes were not recorded in nine of the cases. In the two remaining, no change was noted in one and in the other the reflexes of the extremity were hyperactive.

Vascular Changes.—Of the six cases in which blood pressure readings were recorded in both arms, one showed a slight elevation on the involved side; one, a slight decrease on the affected side; and the remaining four showed no difference between the two recordings. The differential pulse recordings were as follows: stronger on the involved side in one case; weaker on the involved side in two cases; and the same in both extremities in two cases. In the remaining cases, the differential pulse was not recorded.

Roentgenologic Examination.—Bilateral cervical ribs were demonstrated in two cases. Both of these cases presented symptoms on the left side. Unilateral cervical rib was demonstrated in two cases. In both of these cases, symptoms were present on the ipsilateral side, one presenting symptoms on the left and one on the right. It should be emphasized that cervical ribs, when bilateral, are not easy to diagnose unless one is on the alert for the anomaly.

Operative Procedure.—The operative technic in all of the cases was essentially the same as that described by Ochsner, *et al.*³ Scalenotomy alone was done in nine of the cases. Resection of the cervical rib in addition to the scalenotomy was done in one case of unilateral cervical rib; and in one case of bilateral cervical rib, a portion of the rib was removed in addition to the scalenotomy on the affected side. Bilateral scalenotomy was done in none of these cases. Spurling and Bradford²⁴ call attention to the temporary paralysis of the diaphragm in these cases following traction on the phrenic nerve and advise against bilateral tenotomy of the muscle in one stage. Donald and Morton²⁵ and others, however, have performed bilateral scalenotomy at one sitting, without any ill effects.

Operative Results.—All but one of these cases obtained complete relief of symptoms immediately following operation. The longest follow-up period, according to the records, was approximately one year. The one case of bilateral cervical ribs in which the result was poor was still complaining of pain two months following operation.

SUMMARY AND CONCLUSIONS

(1) The scalenus anticus syndrome, in general, is discussed, and 11 cases presenting symptoms of this entity are reviewed.

(2) Seven cases were not associated with a cervical or abnormal rib,

indicating that the scalenus anticus syndrome occurs with much greater frequency than the cervical rib syndrome.

(3) The symptoms are the result of spasm of the scalenus anticus muscle, resulting in compression of the brachial plexus and subclavian artery, with the creation of a vicious circle.

(4) Attention is called to the fact that many cases of scalenus anticus syndrome may, in reality, be secondary to some other underlying primary pathology.

(5) Scaleneotomy may not be necessary in mild cases, conservatism being all that is necessary to bring about permanent relief.

(6) The results following scaleneotomy in the series reported here have been excellent, only one case of bilateral cervical ribs failing to respond to treatment.

REFERENCES

- ¹ Murphy, J. B.: The Clinical Significance of Cervical Ribs. *Surg., Gynec., and Obst.*, 3, 514, 1906.
- ² Adson, A. W., and Coffey, J. R.: Cervical Rib: A Method of Anterior Approach for Relief of Symptoms by Division of the Scalenus Anticus. *ANNALS OF SURGERY*, 85, 839, 1927.
- ³ Ochsner, A., Gage, M., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome. *Am. Jour. Surg.*, 28, 669, 1935.
- ⁴ Gage, I. M.: Scalenus Anticus Syndrome. *Surgery*, 5, 599, 1939.
- ⁵ Todd, T. W.: Cervical Rib: Factors Controlling its Presence and its Size, its Bearing on the Morphology and Development of the Shoulder. *J. Anat. and Physiol.*, 26, 244, 1912.
- ⁶ Jones, F. W.: Variations of the First Rib Associated with Changes in the Constitution of the Brachial Plexus. *J. Anat. and Physiol.*, 45, 249, 1910.
- ⁷ Haven, H.: Neurocirculatory Scalenus Anticus Syndrome in the Presence of Developmental Defects of the First Rib. *Yale Jour. of Biol. and Med.*, 11, 443, 1939.
- ⁸ Pommerenke, W. T., and Risteen, W. A.: The Scalenus Anticus Syndrome as a Complication after Gynecologic Operations. *Amer. Jour. of Obst. and Gynec.*, 47, 395, 1944.
- ⁹ D'Abreu, A. L.: Cervical Rib Syndrome Associated with a Contracting Lesion of the Apex of the Right Lung. *British Jour. Surg.*, 30, 185, 1943.
- ¹⁰ MacFee, Wm. F.: Cervical Rib Causing Partial Occlusion and Aneurysm of the Subclavian Artery. *ANNALS OF SURGERY*, 111, 549, 1940.
- ¹¹ McLaughlin, Jr., C. W., and Popma, A. M.: Intermittent Obstruction of the Subclavian Vein. *J. A. M. A.*, 113, 1960, 1939.
- ¹² Judovich, B., Bates, W., and Drayton, W.: Pain in the Shoulder and Upper Extremity Due to Scalenus Anticus Syndrome. *Amer. Jour. Surg.*, 63, 377, 1944.
- ¹³ Hansson, K. G.: The Cervicobrachial Syndrome. *Arch. Phys. Therapy*, 22, 662, 1941.
- ¹⁴ Reichert, F. L.: Compression of Brachial Plexus: The Scalenus Anticus Syndrome. *J. A. M. A.*, 118, 294, 1942.
- ¹⁵ Smith, B. C.: Thrombosis of Third Portion of Subclavian Artery Associated with Scalenus Anticus Syndrome. *ANNALS OF SURGERY*, 111, 546, 1940.
- ¹⁶ Patterson, R. H.: Cervical Ribs and the Scalenus Muscle Syndrome. *ANNALS OF SURGERY*, 111, 531, 1940.
- ¹⁷ Nachlas, I. W.: Scalenus Anticus Syndrome or Cervical Foraminal Compression. *South. Med. Jour.*, 35, 663, 1942.
- ¹⁸ Falconer, M. A., and Weddell, G.: Costoclavicular Compression of the Subclavian Artery and Vein. *Lancet*, 2, 539, 1943.

- ¹⁹ Semmes, R., and Murphey, F.: The Syndrome of Unilateral Rupture of the Sixth Cervical Intervertebral Disk. *J. A. M. A.*, **121**, 1209, 1943.
- ²⁰ Aitken, A. P., and Lincoln, R. E.: Fracture of the First Rib Due to Muscle Pull, *New England Jour. Med.*, **220**, 1063, 1939.
- ²¹ Freiberg, J. A.: The Scalenus Anticus Muscle in Relation to Shoulder and Arm Pain. *Jour. Bone and Joint Surg.*, **20**, 860, 1938.
- ²² Brown, H. M.: Secondary Scalenus Anticus Syndrome. *U. S. Naval Med. Bull.*, **42**, 1164, 1944.
- ²³ Bishop, W. A.: Calcification of the Supraspinatus Tendon. *Arch. Surg.*, **39**, 231, 1939.
- ²⁴ Spurling, R. G., and Bradford, F. K.: Scalenus Neurocirculatory Compression. *ANNALS OF SURGERY*, **107**, 708, 1938.
- ²⁵ Donald, J. M., and Morton, B. F.: The Scalenus Anticus Syndrome with and without Cervical Rib. *ANNALS OF SURGERY*, **111**, 709, 1940.

EXPERIENCES WITH POSTTRAUMATIC OSTEOMYELITIS IN WORLD WAR II

WILLIS M. WEEDEN, M.D., GORDON McNEER, M.D.,
HYMEN D. STEIN, M.D., AND JOHN C. LONG, M.D.

NEW YORK CITY, N. Y.

OUR PURPOSE in presenting this material is to evaluate, insofar as is possible, our results in the treatment of osteomyelitis in Chinese battle casualties of the North Burma Campaign of 1943-1945. This is an elaboration and continuation of a report already published by Weeden and Stein.¹ Two factors must be first made clear: (1) Definition of osteomyelitis. (2) Method of interpreting end-results.

Chronic infection of the bone resulting from infected compound fractures as a result of trauma is not justly comparable to hemogenous osteomyelitis. The process is far less fulminating and its management proceeds along entirely different lines. Data for practical reporting or statistical analysis was collected from those case histories in which positive statements were recorded; *i.e.*, a roentgenologic diagnosis of osteomyelitis; a report by our pathologist on the nature of the operative specimens; or, a note by the operating surgeon that osteomyelitis or a sequestrum, or both, were encountered. Patients were managed by all of the surgeons in the hospital, and not segregated. Frequent observation and consultation by the Chief of the Surgical Service, however, tended to effect greater uniformity than this description suggests.

An accurate comparison of the results of treatment of the chronic osteomyelitis encountered in World Wars I and II is not intended. The supplementary use of the sulfonamides has encouraged present-day surgeons to attempt primary closures, and, in the opinion of many surgeons, has completely altered the management of the disease, from that encountered in the military hospitals during World War I.

Caldwell² has concluded that the pre- and postoperative use of sulfonamides is indicated when reconstruction of infected fractures is anticipated, because it reduces systemic and local diffusion of infection. However, elimination of local bone infection should not be anticipated. Our impressions justify this conclusion. Yet Dickson, Dendey and Kiene³ reported a series of 22 patients in whom the osteomyelitis was treated by pre- and postoperative sulfathiazole, saucerization, wound closure, and immobilization, with complete healing occurring in 82 per cent of instances on an average of 23 days. Badgley and Harris⁴ described a series of 25 case histories of old nonunited, infected fractures. In the presence of infection definite reconstructive procedures were performed. Wounds were left open, and 72 per cent of cases united and were healed on an average of 13 months. The

obvious difference in the healing period brings up the whole question of whether such wounds may be closed safely, now that the sulfonamides are available.

In 1944, Key⁵ began the treatment (over a 2.5-year period) of 101 consecutive cases of osteomyelitis, administering sulfathiazole for five days pre and 15 days postoperatively. The tibia was involved in 33 instances, the femur in 24, and other bones in 44. Including 11 amputations, 60, or 59.4 per cent, healed *per primam*. The reports are not classified as to the percentage of healing occurring in each bone studied, and the inclusion of amputations seems unwarranted.

Tourney⁶ reported the cases of 13 patients very similarly managed, with healing in ten instances, or 76.8 per cent. The series is small, and a comparison of healing in upper and lower extremity lesions is, again, not reported.

That chronic infection, associated with retained sequestra or foreign bodies, is often sulfa-resistant, and that the debilitated status of many patients may contraindicate sulfonamide therapy was well-recognized by Lyons.⁷ Both Speed⁸ and Baker⁹ concluded that the local use of sulfonamide is of help in combating infection, only when the fundamental rules of wound hygiene have been followed. Baker rightly asks what results might be obtained from adequate surgery without chemotherapy, because of the relative lack of improvement from the addition of sulfonamide to the open method. After a study of data gathered from the case histories of 2,191 patients, 674 compound fractures, Meleney¹⁰ came to a conclusion somewhat similar to that of Speed and Baker.

In these patients the chief factors concerned with the development of infection were found to be as follows:

1. The degree and extent of tissue damage.
2. The degree of gross contamination by dirt and other foreign bodies.
3. Time-interval between injury and initiation of surgical care.
4. The nature of the bacterial contamination of the wound.
5. The care and thoroughness with which the devitalized tissue, foreign bodies and gross contamination were removed from the wound.

Meleney¹⁰ could not demonstrate that sulfonamides, locally or systemically, materially reduced the incidence or severity of local infections, or eliminated the pathogenic organisms from the wounds. Spread of local infection was minimized, however, and hence the incidence of septicemia and death decreased, when the drug was administered by systemic means.

The bulk of the evidence, therefore, seems to force us to conclude that the addition of the sulfonamides to our armamentarium in the treatment of chronic osteomyelitis has had its greatest value when employed systemically, and acts in the following manner:

1. The disease remains as a localized process in the bone involved, instead of producing a fulminating and disseminating process.

2. Preoperative sulfonamide therapy will frequently decrease the infection of the adjacent soft tissues, and sometimes clear it up entirely.

Improvement and standardization of sound surgical principles are still of the greatest importance in the management of the local infection of soft tissues and bone.

The material upon which this report is based consisted of 365 Chinese soldiers, almost all of whom fought in the Hukawng and Mogaung Valleys, and between Myitkyina and Bhamo along the Irawaddy River in the North Burma campaign of 1943-1945. Whereas, they are a sturdy race, many of the soldiers were afflicted with chronic malnutrition, malaria, dysentery and venereal diseases. The recurrence of malaria after any operative procedure was quite frequent, and it is hard to believe that chronic diseases did not have some deleterious effect on wound healing.

TABLE I
RESULTS

Bones	Total	Per Cent	Healed at 3 Months	Per Cent	Hosp. Av.	Full Duty	Per Cent	Limited Duty	Per Cent	Disab. Duty	Per Cent
Tibia.....	76	20.7	36	47.3	10.3	46	60.5	14	18.4	16	21.0
Femur.....	64	17.7	17	26.5	7.2	35	54.6	5	7.9	24	37.5
Humerus....	50	13.6	21	42.0	6.4	27	54.0	11	22.0	12	24.0
Ulna.....	28	7.6	14	50.0	5.5	18	64.3	8	28.5	2	7.1
Radius.....	26	7.1	16	61.5	8.8	16	61.5	5	19.2	5	19.2
Phalanges....	23	6.3	12	52.2	3.8	18	78.2	3	13.0	2	8.7
Metatarsals...	22	6.0	7	31.8	5.5	10	45.5	4	18.1	8	36.2
Pelvis.....	14	3.8	6	42.8	5.9	11	78.6	1	7.7	3	21.3
Ribs.....	13	3.5	7	53.9	5.1	10	76.9			2	15.4
Metacarpals..	12	3.3	9	75.0	4.5	11	91.6			1	8.3
Fibula.....	12	3.3	7	58.3	5.9	7	58.3			5	41.6
Os calcis.....	9	2.5	2	22.2	6.7	8	88.8			1	11.1
Scapula.....	8	2.2	4	50.0	3.8	5	62.5	2	25.0	1	12.5
Sternum.....	4	1.1	2	50.0	5.5	3	75.0			1	25.0
Carpals.....	4	1.1	3	75.0	8.3	3	75.0			1	25.0
Clavicle.....	3	0.8	2	66.7	6.0	2	66.6			1	33.3
Total.....	368	100.0	165	44.8	6.2	230	62.6	53	14.5	85	23.0

The diagnosis of osteomyelitis, as we have defined it elsewhere, was established in every instance by radiographic means, the presence of infected bone and marrow, or the removal of a sequestrum. Whereas, it might theoretically be advisable to divide our study into that of frank osteomyelitis and sequestration, for practical purposes the same disease exists in both instances. Hence, no attempt will be made to differentiate between the end-results of each, since the extrusion or removal of a single sequestrum by no means guarantees cure.

Although such information was not always found on the accompanying slips or charts, we presumed that all cases received débridement and encasement in the Portable Surgical Hospitals and Aid Stations in the Forward Area. Many of them must have been given a variable amount of one of the sulfonamides.

Osteomyelitis of the skull, jaws and vertebrae is not included in this study.

Analysis.—It is readily seen that the tibia is by far most commonly injured and involved by infection. Likewise, the healing period (10.3 months) from injury to discharge on duty status is considerably longer than that of the humerus (6.4 months), or femur (7.2 months). This is probably due to its subcutaneous position and often inadequate and compromised blood supply.

The bones of the forearm, particularly the radius, are seen to respond fairly well to surgery.

REOPERATIONS REQUIRED

Radius.....	3.8%
Ulna.....	7.1%
Femur.....	18.7%
Tibia.....	26.3%
Humerus.....	16.0%

Here, again, the necessity for reoperations is seen to be far higher in the case of the lower extremity than in the upper.

Primary Closure.—When adequate soft tissue was available the closed method was applied to those cases. This type of wound management was employed in 69 instances. Patients were routinely given sulfonamide gr. 15

TABLE II
RESULTS OF PRIMARY CLOSURES OF WOUNDS
SUCCESSSES

Bone	No.	Healed	Prim.	Secondary		Total		Failures	
Femur.....	9	2	22.2%	4	44.4%	4	66.6%	3	33.3%
Tibia.....	16	9	56.2%	3	18.3%	12	74.5%	4	25.0%
Humerus	12	8	66.6%	2	16.6%	10	83.4%	2	16.6%
Radius.....	9	5	55.5%	3	33.3%	8	88.8%	1	7.5%
Ulna.....	9	2	22.2%	4	44.4%	6	66.6%	3	33.3%
Scapula.....	2	2	100.0%			2	100.0%	0	0.0%
Phalanges.....	4	3	75.0%			3	75.0%	1	25.0%
Carpal.....	3	3	100.0%			3	100.0%		
Metacarpal.....	2	2	100.0%						
Pelvis.....	3	2	66.6%	1	33.3%	3	100.0%		
Total.....	69	38	55.2%	17	24.6%	55	79.8%	14	20.3%

four times daily for three to four preoperative and about seven to fifteen postoperative days. Plaster encasement was applied in all instances. A definite attempt was made to remove all infected tissue both soft and osseous. Wherever possible adjacent muscles were approximated closely to the defect and a pressure dressing applied. Our results in the case of these 69 patients were as follows:

Primary healing.....	38	55.2%
Secondary healing.....	17	24.6%
	55	79.8%
Failures.....	14	20.3%

The results of employment of primary closure was thus satisfactory in 79.8 per cent of patients so treated. As regards wound healing (Table II) the total length of hospitalization before return to duty status was not

POSTTRAUMATIC OSTEOMYELITIS

appreciably shortened (Table III), except in the case of those patients in whom the ulna alone was involved. The most significant advantage of the closed method lies in the fact that a definitely larger percentage of patients was returned to full duty (Table IV) when the femur, tibia or humerus were involved by osteomyelitis. Wounds of the forearm were complicated by injuries to numerous important adjacent structures to such an extent that a return to duty status was less frequently possible (Table V).

Three patients (0.82 per cent) died subsequent to operative treatment. One of these had far-advanced (Grade IV) pulmonary tuberculosis. His death occurred 12 days after total scapulectomy, at which time the operative

TABLE III
COMPARISON OF HOSPITALISATION
PRIMARY CLOSURES AND OPEN CASES

Bone	Primary	Open
Femur.....	7.2 months	7.5 months
Tibia.....	6.5 months	6.6 months
Humerus.....	5.2 months	5.7 months
Radius.....	8.2 months	7.8 months
Ulna.....	5.0 months	7.4 months

TABLE IV
COMPARISON OF FULL DUTY STATUS
PRIMARY AND SECONDARY METHODS

Bone	Total Cases	Cases to Duty	Closures (Primary)	Closures to Duty	% to Duty	Total Open	Open to Duty	% Open to Duty
Femur.....	64	35	9	8	88.8	55	27	49.0
Tibia.....	76	46	16	7	43.7	60	39	65.0
Humerus.....	50	27	12	7	58.3	38	20	52.6
Ulna.....	28	18	9	5	55.5	19	13	68.4
Radius.....	26	16	9	3	33.3	17	13	76.4

wound was clean. The two remaining deaths occurred in patients who had extensive osteomyelitis of the ribs. In each case the original trauma had involved intrathoracic organs, and the patients died of intrapleural infection.

OPERATIVE MANAGEMENT

1. Because of extensive hemorrhage, whenever possible, a tourniquet was applied well proximal to the operative site, and extremely hot packs were available. Upon only a few occasions were pressure packs left in the wounds, and these were removed in two to three days.
2. Whenever curettage of the femur was contemplated, infusions of glucose or saline were started. Plasma was always available, but so great was the shock at times that transfusions of whole blood rapidly forced into the femoral vein were required. We are certain that this form of management prevented many accidents which might have cost the patient his life.
3. Strict adherence to the Orr-Trueta principle, as practised in the Forward Area, is not recommended in the Rear Echelon. Long periods of

immobilization often result in poor circulation of blood and lymph, skin damage, muscle atrophy and stiffness of joints. Wherever there was no danger of pathologic fracture, the plaster encasement was removed three weeks, postoperatively, and the wound treated by infrequent dressings. Earlier return of function resulted from this form of management.

Physiotherapy was often relatively ineffective as the individual soldier, because of pain, could not be convinced of the necessity of doing anything for himself in the way of active motion. As a consequence, many of the Chinese patients will not obtain the functional result expected in American patients.

TABLE V
COMPLICATIONS

Bone	Nerve Lesion	Soft Tissue Lesion	Tendon Lesion	Muscle Lesion	Bone Graft	Poor Function	Pain-ful Gait	Pain-ful Scar	Ankyl-osis	De-formity	Others
Femur.....							2	2	Ankle 6		Nonunion 1
									Knee 1		Hysteria 1
Tibia.....	Perineal 2				2	4		8	9		Hysteria 1
Fibula.....			1			3			1		
Metatarsals.....		2							2	2	Causalgia 1
Os calcis.....							4	1			
Pelvic bones.....							1				Pyarthro-sis 1
Scapula.....						1		1			TBC, Causalgia 1
Clavicle.....											Pyarthro-sis 1
Sternum.....											Causalgia 2
Humerus.....	Radial 9			3	3				4		TBC, 1
	Median 1										
Radius.....	2	1	3		5				1		
Ulna.....	2	1	2		3				1		Cross-union 1
											Lues 1
Carpals.....	1		3								
Metatarsals.....		1						3	1		
Phalanges.....		1			1	2			1		
Ribs.....											Pleural comp., and death (TBC.) 2

SUMMARY

1. A report of 368 cases of osteomyelitis in Chinese soldiers is herein summarized.

2. The tibia is most frequently involved, followed by the femur and ulna.

3. Radical débridement of diseased soft and osseous tissue and good surgical toilet is imperative if a definitive arresting of the disease is to be attained.

4. Employment of sulfonamides systemically probably results in a more localized pathologic process, and, certainly, prevents dissemination of the disease. The rationale of local use of sulfonamides is doubted.

5. Primary closure is recommended in the management of osteomyelitis when adequate soft tissue is available. Otherwise, the open method is advocated.

6. Early removal of the plaster encasement is recommended where pathologic fracture is not apt to follow such management, to permit earlier recovery of skin, soft tissues, circulation and joints.

REFERENCES

- ¹ Weeden, Willis M., and Stein, Hymen D.: Experiences with Injuries and Diseases of Bone in World War II. *ANNALS OF SURGERY*, 122, 23, 1945.
- ² Caldwell, Guy A.: Lectures on Reconstructive Surgery. American Academy of Orthopedic Surgeons, 1944.
- ³ Dickson, F. D., Dendey, R. L., and Kiene, R.: The Use of Sulfathiazole in Treatment of Subacute and Chronic Osteomyelitis. *Journal of Bone and Joint Surgery*, 23, 516, 1941.
- ⁴ Badgley, C. E., and Harris, H. W.: Treatment of Ununited Infected Fractures. *Journal of International College of Surgeons*, 3, 413, 1940.
- ⁵ Key, J. Albert: Sulphonamides in the Treatment of Chronic Osteomyelitis. *Journal of Bone and Joint Surgery*, 26, 63, 1944.
- ⁶ Tournay, James W.: Sulphathiazone in Chronic Osteomyelitis. *Surgery* 14, 531, 1943.
- ⁷ Lyons, C.: The Evaluation of Sulpha Drugs. *Military Surgeon*, 95, 301, 1944.
- ⁸ Speed, Kellogg: The Treatment of Open Fractures. *International Abstracts of Surgery*, 77, 1, 1943.
- ⁹ Baker, L. D.: Sulfonamides in Traumatic and Infected Wounds. A Report of their Use in Fresh Compound Fractures, Old Compound Fractures, Fractures with Infection and Chronic Osteomyelitis. *Journal of Bone and Joint Surgery*, 24, 641, 1942.
- ¹⁰ Meleney, Frank L.: Statistical Analysis of a Study of Prevention of Infection in Wounds, Compound Fractures, and Burns: With Special Reference to the Sulphonamides. *Surgery, Gynecology and Obstetrics*, 80, 263, 1945.

BONE GRAFTING METHODS

TWO ILLUSTRATIVE CASE REPORTS

PAUL C. COLONNA, M.D.

PHILADELPHIA, PA.

EVOLUTION OF BONE GRAFTING during the past 100 years is a fascinating story. The bitter controversy that waged about the monumental work of Macewen and Ollier regarding the rôle that periosteum plays is still not completely settled. It is interesting to note that the 3-year-old child upon whom Macewen illustrated his most striking experiment in the problem of bone grafting was done by packing chips of bone into the sleeve of the periosteum which remained after the humeral shaft had been excised because of a long-standing osteomyelitis. At present, the common method of grafting consists in using either the intermedullary, inlay or the various types of onlay graft. We are only beginning now to appreciate the tremendous value of utilizing bone chips and masses of cancellous bone packed about the graft.

In all bone grafting operations the following are desired: First, excision of avascular scar tissue as far as is consistent with good surgery, and this includes both osseous and soft-tissue and the use, sometimes, of preliminary skin grafting; second, operation in as clean a field as possible; third, immobilization by firm fixation of the graft to the proximal and distal bone to be bridged; fourth, adequate support and splinting which should be continued during the restoration of function of the part; and fifth, roentgenologic evidence of solid bony union.

The "massive" bone graft term was apparently first popularized by Henderson, and the principle has been employed in the two cases herein reported. The bridging of the large defects can be accomplished by the use of the split-graft or the whole-graft. In the two cases herein reported each method is demonstrated.

CASE REPORTS

Case 1.—Mrs. S., age 30, gave a history of having injured her right knee in December, 1931 and February, 1932, followed by swelling and pain. On March 10, 1932, she was operated upon. A giant cell tumor of the lower end of the right femur was found, and verified by pathologic report. From March, 1932 until February, 1945, the patient had a number of different treatments to the knee. During the 13-year period the wound had never healed, and she has received radiation implantation into the wound, seven curretages and a long course of roentgenotherapy. She presented chronic suppurative osteomyelitis, with a large, draining, foul-smelling sinus in the region of the external condyle of the femur. Culture revealed *hemolytic Streptococcus* and *Staphylo-*

* Cases presented at Joint Meeting of the New York Surgical Society and Philadelphia Academy of Surgery, College of Physicians, Philadelphia, February 13, 1946.



FIG. 1.—Case 1: On admission to the University Hospital, showing extensive chronic osteomyelitis before resection. Gross specimen showed no evidence of previous giant cell tumor but necrotic shell of bone.

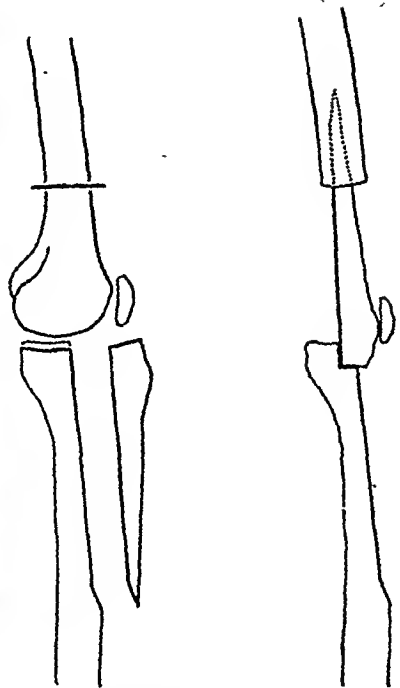


FIG. 2.—Showing diagram of steps of operation.



FIG. 3.—Showing massive tibial bone graft in place after removal of transfixion pins put in at time operation.



FIG. 4.—Showing bony union, proximally and distally, of tibial graft one year after operation. Note increase in growth of graft and callus formation

coccus albus. She retained about 10° motion in the knee and walked with crutches, complaining of pain constantly.

On February 20, 1945, she was admitted to the Orthopedic Service at the University of Pennsylvania Hospital, and, on February 28, 1945, a resection of the distal 13 centimeters of the femur was done. A massive tibial graft was removed from the tibia, and placed in position shown in diagram. Technically, the operation was not difficult and was done under tourniquet. The knee joint was approached by a medial patellar incision after carefully blocking the cavity with sterile dressings and incising the skin about the periphery of the sinus, sealing-off as far as possible the infected draining area. After opening the knee joint, a midline incision was then made over the anterior surface of the femur through the vastus intermedius muscle, exposing the shaft of the femur. The entire cortex of the femur up to the site of anticipated division was exposed by stripping the muscles subperiosteally. A Gigli saw was gently introduced around the bone and this was divided 13 centimeters above the knee joint. The entire distal portion of the femur was then shelled out of its bed and separated from its muscular and ligamentous attachments. The cartilage from the upper articular surface of the tibia was removed and a large, long graft consisting of approximately half the thickness of the

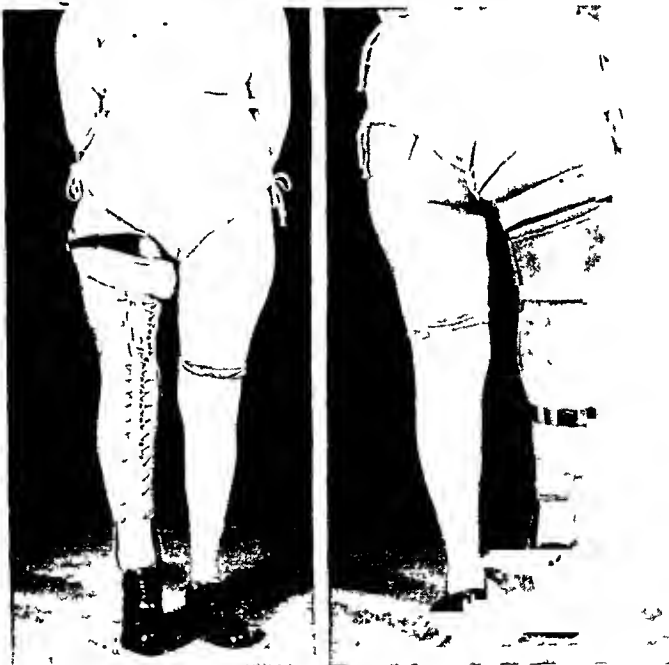


FIG. 5-A

5-B

FIG 5-A.—Present brace patient is wearing (front view).
5-B.—Present brace patient is wearing (back view).

BONE GRAFTING METHODS



FIG. 6.—Case 2: On admission to University Hospital after four unsuccessful attempts to obtain bony union. Note useless position of hand with prominence of ulna styloid.

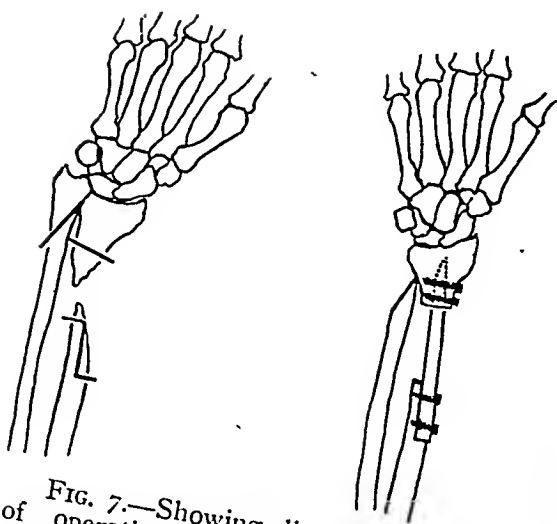


FIG. 7.—Showing diagram of steps of operation using whole-thickness fibula graft.



FIG. 8.—Showing graft in position held with four vitallium screws.

tibia removed and turned upward, inserting the distal end of the graft into the intramedullary cavity of the femur and the opposite end in the prepared bed in the tibia. The graft was held in position by Steinman pins which protruded through the skin and were later incorporated in the plaster. The wounds were then closed in layers, both the anterior and lateral wounds and a plaster spica applied. The pins remained in for six weeks and were removed when the plaster was changed. About seven months after the massive bone graft operation a walking-iron was fitted into the spica and the patient allowed to bear weight. Ten months after operation all plaster



FIG. 9

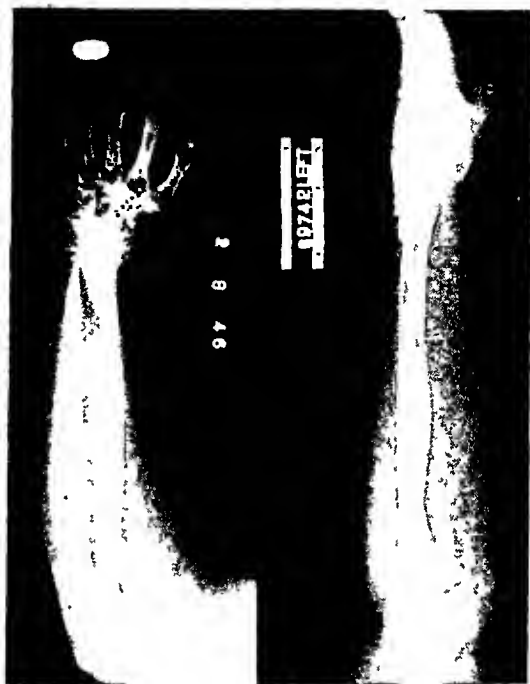


FIG. 10

FIG. 9.—One and one-half years postoperatively, showing site of removal of fibula graft. No disability whatsoever.

FIG. 10.—One and one-half years after whole-thickness fibula graft and Darrach operation upon ulna; resulting in normal rotation and good symmetry to the wrist.

was removed and she was fitted with a pelvic ring, long leather cuff-type of brace, as shown in diagram. Roentgenograms before and after operation are shown.

The patient is now walking about with the aid of a brace and apparently has solid bony union at the proximal and distal portion of the graft, as shown in Figure 9, approximately one year after operation.

Case 2.—R. A., female, age 49, gave a history of having fallen, May, 1942, and fractured her left radius and ulna styloid process. The fracture was treated by her physician, and on removal of plaster six weeks later, a nonunion was noted. Following this she had three attempts at obtaining union by open operation, without success.

When she was first seen by the writer, December 16, 1943, she presented the picture as shown in Figure 1. The hand was markedly deviated, the ulna was very prominent and frank nonunion was noted. Marked thickness of the wrist, loss of function in the fingers of the hand, and complete loss of pronation and supination were noted. On July 11, 1944, she was admitted to the Orthopedic Service, at the University of Pennsylvania Hospital, and, July 12, 1944, a whole-thickness fibula graft

was used. It was decided to use this type of graft in order to preserve a complete cortical surface, believing that a freer gliding motion of the tendons could thereby be expected.

The operation was as follows: Under a blood pressure cuff the Darrach operation was first done, excising the distal portion of the ulna. Another incision was made over the radial aspect and the sclerotic ends of bone at the site of nonunion along with the wire that had been placed there in a previous operation were removed. All scar tissue of the soft-part had to be totally excised. When this was completed there was a gap of about two and one-half inches between the radial ends, and when traction was made on the hand to correct the radial deviation, a good three inches remained to be bridged. The middle third of the fibula on the same side was then removed subperiosteally. The graft was driven into the distal fragment and attached to the proximal fragment, as shown in the diagram, and held in place by four vitallium screws. Plaster was applied from the fingers to the middle of the arm, with the elbow at a right angle and the hand in slight ulnar deviation. The wound healed *per primam* and subsequent roentgenograms showed continued evidence of solid bony union. Three months after the operation all support was removed. On January 11, 1945, she was admitted to the hospital for removal of the screws and, as shown by roentgenograms, she had solid bony union. A roentgenogram of the defect in the fibula caused by the removal of the graft is shown. This is not giving her any trouble and has not resulted in any disability whatsoever. At present, one and one-half years after the operation, she has a practically normal range of rotation and finger motion, with very slight limitation in the movements of the wrist.

EXPERIMENTAL OBSERVATIONS ON ABSORBABLE ALGINATE PRODUCTS IN SURGERY*

GEL, FILM, GAUZE AND FOAM

MAJOR GEORGE BLAINE, R.A.M.C.

SUTTON, SURREY, ENGLAND

LATE OF THE BIOLOGIC RESEARCH STAFF POOL, WAR OFFICE

IMPORTANT ADVANCES have been made in the prevention of adhesion formation in the course of tissue repair, the arrest of capillary hemorrhage and the closed treatment of burns during the war years through the development of new materials.

Fibrinogen products from plasma in the form of film, foam, and with the aid of thrombin, into clot, were prepared by the various Departments at Harvard University.^{1, 2} As a film, it is stated to fulfill the requirements of an absorbable tissue isolator,³ keeping injured tissues apart in course of their healing; applied as foam or solution to an oozing surface, combined with either added or locally produced thrombin it arrests hemorrhage,³ and painted or sprayed in a glycerol plasticized solution on a wound or burn it gives a flexible, impermeable cover.²

Cellulose compounds and polyvinyl plastics were used in experiments by Frantz,⁴ at Columbia University, New York. The grades of polyvinyls used proved too irritable to tissue and nonabsorbable; oxidised cellulose (oxycellulose), however, was stated to be useful. It sets up a minimal fibrous tissue reaction and becomes absorbed in tissue.⁴ Putnam⁵ made use of this soluble cellulose, combined with thrombin, in neurosurgical operations, and reported satisfactory results; other satisfactory results were reported by Frantz and Lattes,⁶ who submitted oxycellulose gauze to clinical trial for the arrest of capillary hemorrhage.

Casein films formed *in situ*, methyl cellulose, and polyvinyl chloride films were recommended by others for the treatment of extensive burns.⁷

None of these materials are free from disadvantages. Fibrinogen and oxycellulose are not sterilizable by current methods, using heat and pressure; their sterilisation is by the formalin method and, consequently, bacteriologic control is necessary. Oxycellulose was found to be incompatible with penicillin. Casein films in burns need an additional impermeable cover. Polyvinyl chloride and methyl cellulose film are nonabsorbable, and their use is, thus, restricted to external application.

The introduction and description of a new material for these purposes can be warranted only if it shows conspicuous advantages over those used at present. It must be absorbable at a readily controllable rate. The tissue reaction caused by it must compare favorably with protein films and with oxycellulose.

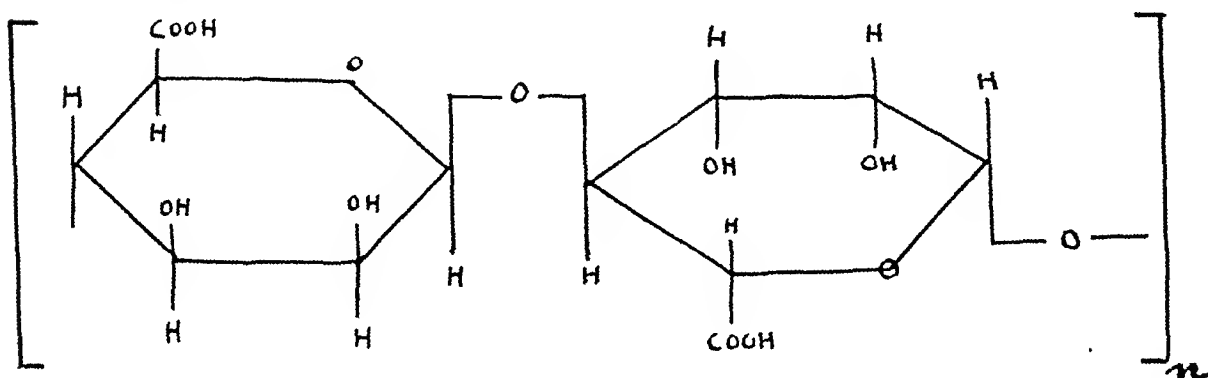
* Submitted for publication January 29, 1946.

Mr. C. W. Bonniksen, Chief Chemist of Alginate Industries Limited, Maidenhead, Berkshire, England, is to be thanked for samples of alginates and all technical information.

It should be easier and cheaper to produce than, say, fibrinogen plastics. It must be compatible with penicillin and other antibacterial substances. It must allow sterilization by current routine methods. Its physical properties must allow modification of plasticity. Finally, it ought to be able to "carry" substances ensuring their controlled, delayed absorption in the organism.

Such an ubiquitous material has been found in the extract of the brown seaweeds. This extract—alginic acid—is yielded alone on hydrolysis of this type of seaweed.

Alginic acid is a polymer of d-mannuronic acid. It was discovered by Stanford,⁸⁻⁹ in 1882, in course of kelp extraction experiments in Scotland. Its formula bears a striking resemblance to that of cellulose, with the difference that the alcoholic group is here replaced by the carboxyl group ($C_6H_{10}O_7$). By the control of the rate of hydrolysis a wide viscosity range is possible, *viz.* from Grade 6 to Grade 1,000, representing a mean molar mass of 25,000 to 200,000.



Photograph showing the molecular structure of alginic acid.

Many salts can be prepared from alginic acid. The acid itself is not soluble in water; some of the organic bases and the salts of the alkali metals are. The other inorganic bases are insoluble.

The sodium salt of this acid, sodium alginate ($NaAlg$), when acted upon by ionic calcium, undergoes instantaneous coagulation. This reaction is the basis of preparing clot, film, filament (from which gauze can be woven) or foam. A certain limited range of "rigid" plastics objects can also be prepared with some modification of technic.

The reaction which takes place is according to the formula— $2NaAlg + CaCl_2 \longrightarrow CaAlg_2 + 2NaCl$ —which reaction is reversible, *in vitro*, by double decomposition, thus, $CaAlg_2 + Na_2CO_3 \longrightarrow 2NaAlg + CaCO_3$.

Sodium alginate is supplied as a granular or fibrous powder in various Grades. When stirred into water it tends to lump and a high speed stirrer is, therefore, useful in the preparation of the solution. Owing to enzymic decomposition, if left standing at high atmospheric humidities, and the danger of bacterial growth, solutions to be kept for any period should have 0.1% phenol or formaldehyde added. If it is desired to "time" the reaction, a suspension of calcium sulphate is used which coagulates sodium alginate slower than calcium chloride. The incorporation of calgon (sodium hexametaphosphate) controls the reaction. At an acid pH coagulation is quicker than at an alkaline pH .

The moisture-holding capacity of alginates is high, of the order of 18-20%. The salts are relatively stable at ordinary temperatures, and humidities, but when wetted, they become subject to attack by certain moulds and enzymes.

Although salts of metals other than of calcium can be used to coagulate alginates, calcium alginate has so far been found to be most useful, as its degree of contraction on drying is lowest; it has excellent film-forming properties; filaments of calcium alginate can be easily prepared by extruding a viscous solution of sodium alginate through jets passing through a bath of coagulant, such as calcium chloride.

Calcium alginate will absorb its own weight of water or even more, under favorable conditions. Other salts like zinc, aluminum, chromium and beryllium alginates are less susceptible to swelling.

The faculty of coagulation of sodium alginate by calcium salts is very sensitive. The reaction takes place with solutions of sodium alginate of the order of 0.1 per cent and of calcium chloride of 0.1 per cent, the higher the molecular weight and concentration of sodium alginate and the higher the percentage of the calcium salt used, the firmer and tougher clot, or film, or filament is obtained. It must be borne in mind, however, that solutions of over five per cent are unworkable.

The sensitivity of the clotting mechanism of sodium alginate with a calcium salt allows the "mixing in" of a high proportion of other solutions, such as plasma. Coagulation was obtained with 90 parts plasma added to ten parts of five per cent sodium alginate solution, reacted upon by concentrations of calcium chloride from 0.5 per cent upwards, or by using a tenth-molar solution of calcium glycerophosphate. The reaction can, therefore, be used as a clotting reaction for plasma. Filaments containing up to 20 per cent plasma or 20 per cent casein were also prepared. These were of a higher tensile strength, but of a lower wet strength and knotting strength, than calcium alginate filaments.

Physical Properties of Alginate Gel, Film, Gauze and Foam: (A) *Gel*: When sodium alginate and calcium chloride are reacted to form a clot, this clot is soft, pliable and, on squeezing, excess calcium can be expressed. If allowed to dry, the clot contracts to a very small size and becomes pearly hard in 48 hours at room temperature at a low humidity of the air. Thus, for instance, if a big drop of sodium alginate is carefully dropped into a pool of calcium chloride, a spherical "pearl" of calcium alginate forms at once, with a mean diameter of approx. 1-2 mm. If this sphere is now exposed to drying at room temperature at a low moisture grade, in 48 hours it contracts to the size of a pinhead, with a mean diameter of approximately 0.1 mm. In this stage it can be sprayed similar to salt, through the openings of a rather coarse salt container. Placed in water, it will regain its former size in about 48 hours. In spite of its hardness it becomes absorbable in the organism.

(B) *Film*: Calcium alginate film can be prepared in any thickness. A film, say, 10-30 mu. in thickness, when dry, is tough, somewhat brittle, but with a fair degree of tensile strength. Placed in water it is made pliable. The addition of plasticisers, *e.g.*, glycerol, yields an absorbable film which is already plastic in its dry state exhibiting none of the brittleness of dried calcium alginate. On the whole, the films are not unlike various grades of cellophane with which they share absolute transparency.

(C) *Filaments*: Filament yarns of two varieties can be prepared, namely; monofilaments and polyfilaments. In the former, extrusion takes place through a comparatively large-sized "spinnerette," and the filament thus obtained is made of one fiber. In the latter, a number of very thin filaments are extruded and twisted upon one another to form composite fibers of up to 200 individual fibers.

The tensile strength of the filaments is of the same order as viscose. The great reduction of strength on wetting renders calcium alginate filaments unsuitable as a surgical suture.

(D) *Gauze*: Gauze is woven from calcium alginate polyfilaments. The gauze exhibits physical properties similar to ordinary surgical gauze; its absorbent power and bursting strength is approximately 80 per cent of strong Hessian (closer woven); alginate cloth has an even higher strength.

(E) *Foam*: The calcium alginate foam swells in water but does not become waterlogged.

Sterilization: All alginate products subsequently used in physiologic experiments were submitted to a routine bacteriologic control. Tests were also carried out with alginate products previously inoculated with bacteria. The following table shows the results of these tests:

Material	Inoculum	Culture Medium	Method
Sodium alginate powder	<i>Staph. aureus</i> and <i>B. sporogenes</i>	Nutrient broth 37° C., 48 hrs.; and Robertson's meat broth 37° C., 3 days, respectively	Autoclave for 20 mins at 15 lb./sq.in. pressure
5 per cent Sod. alginate sol.	<i>Staph. aureus</i> and <i>B. sporogenes</i>	Nutrient broth 37° C., 48 hrs.; and Robertson's meat broth 37° C., 3 days, respectively	Autoclave for 20 mins. at 15 lb./sq.in. pressure
Calcium alginate film	<i>Staph. aureus</i> and <i>B. sporogenes</i>	Nutrient broth 37° C., 48 hrs.; and Robertson's meat broth 37° C., 3 days, respectively	Autoclave for 20 mins. at 15 lb./sq.in. pressure
Calcium alginate gauze	<i>Staph. aureus</i> and <i>B. sporogenes</i>	Nutrient broth 37° C., 48 hrs.; and Robertson's meat broth 37° C., 3 days, respectively	Autoclave for 20 mins. at 15 lb./sq.in. pressure
Calcium Alg./plasma sheet	<i>Staph. aureus</i> and <i>B. sporogenes</i>	Nutrient broth 37° C., 48 hrs.; and Robertson's meat broth 37° C., 3 days, respectively	Autoclave for 20 mins at 15 lb./sq.in. pressure

Result: All the above materials were found sterile after this treatment. There was no impairment of physical properties of the respective products.

Biochemic: Various grades of sodium alginate were found to accelerate the sedimentation rate of red blood cells. The higher the molecular weight, the more marked was this reaction. Injected intravenously into rabbits, 75 mg./Kg. of sodium alginate, *per se*, was not toxic,¹⁰ if a calcium chloride solution (6 mg./Kg.) was injected intravenously within ten minutes following the injection of sodium alginate, however, the animals invariably died. There is no record available, as yet, whether delayed injection of calcium chloride had the same action.

When sodium alginate and calcium chloride were injected into muscle or the peritoneal cavity, no toxic reaction followed. Noninterference of either sodium alginate or calcium alginate with enzymic activity *in vitro* was also demonstrated.¹¹

On applying sodium alginate to a pool of blood, a rapid and marked syneresis was noticed. Films showed rouleaux formation or aggregation of red blood cells of true hemoagglutination type. This phenomenon was found to be in inverse ratio to the viscosity of sodium alginate used.

Tried as a plasma substitute, sodium alginate solutions clumped red blood cells *in vitro* and *in vivo*. It was, therefore, useless as a substitute material in transfusion.¹⁰

Gough¹² found that the injection of sodium alginate into bronchi in cases of pulmonary tuberculosis successfully blocked tuberculous cavities with no ill effects to the patient.

Physiologic: A number of experiments were carried out to establish the behavior of calcium alginate in animal tissues.

Complete absorption of all alginate products was established in every case. There was no qualitative difference in the biologic properties of alginate products. "Pearls" of calcium alginate absorbed in the same way as did film or gel.

The experiments can be tabulated as follows:

1. Behavior of clot formed by sodium alginate and calcium chloride injected into tissue.
2. Behavior of prepared calcium alginate film inserted into tissue.
3. Behavior of locally clotted calcium alginate and of calcium alginate plasticized with plasma on denuded surfaces.
4. Behavior of calcium alginate gauze in internal hemorrhage.

(1) *Calcium Alginate Clot Formed in situ, by Injection:* In this series rabbits were used. The method adopted was as follows: The injection of the two reacting substances was made through separate syringes and needles to prevent clotting in the syringe or needle. A wide-bore needle was used to inject the viscous sodium alginate solution. The materials used were 3 cc. each of 5 per cent sodium alginate and 2 per cent calcium chloride. Sodium alginate was injected first; the calcium chloride was injected into the mass of sodium alginate. A clot was palpable immediately. The site of injection was the rectus femoris muscle. As controls, 5 per cent sodium alginate was injected in one group, and 2 per cent calcium chloride in another.

Sections were taken from the respective sites a week, or longer, after the injection. The animals were anesthetized by intraperitoneal nembutal.

While the control animals showed no trace of any injected substance, and no clots were palpable at any time during the experimental period, those injected with the combination of sodium alginate and calcium chloride had a palpable clot at the injected site 24 hours after the injection. This clot was easily palpable for a few days, after which period it gradually disappeared. The average final disappearance was 10-14 days.

FIG. 1.—Photograph of various alginate products.

- (A) Calcium alginate cloth.
- (B) Calcium alginate yarn (polyfilament).
- (C) Calcium alginate film.
- (D) Calcium alginate gauze.

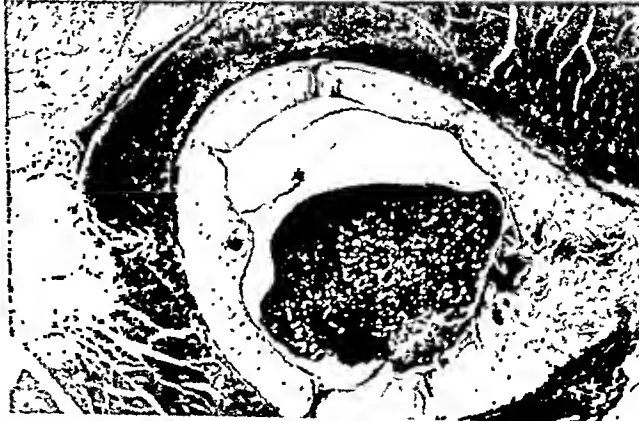
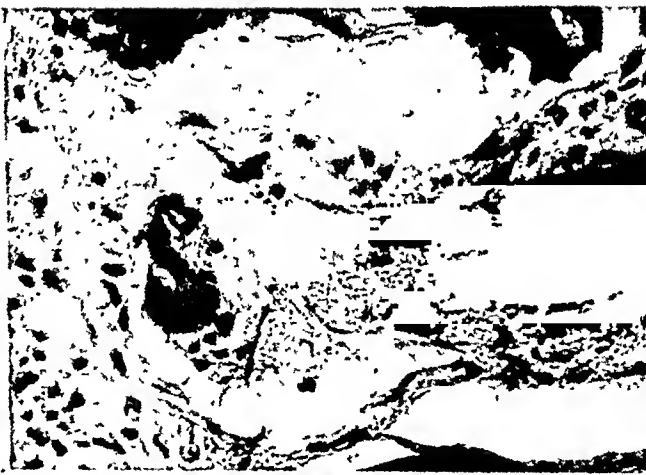
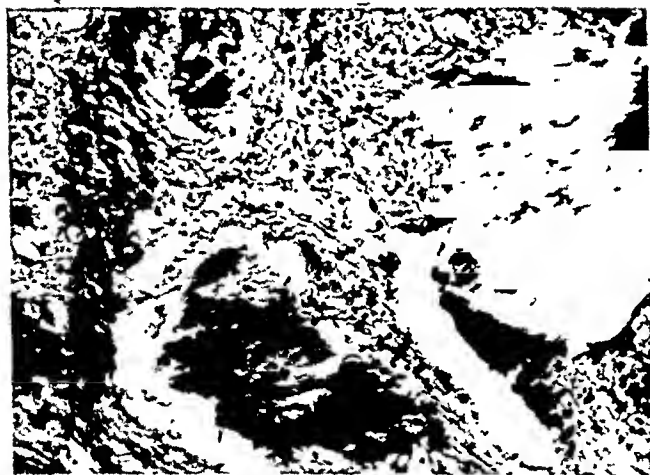
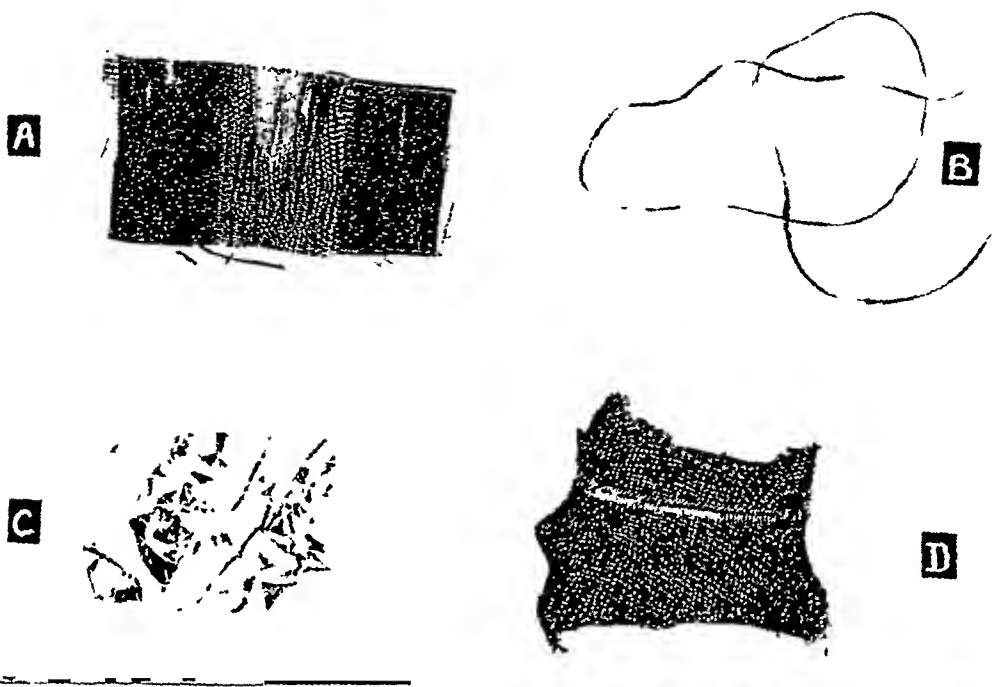
FIG. 2.—Remains of calcium alginate clot at seven days. The dark amorphous masses are calcium alginate. The margins of the masses are seen to be penetrated and fragmented by invasion of polymorphonuclear leukocytes. No giant cells are present.

FIG. 3.—Calcium alginate clot at 14 days. The small amorphous clot is seen in the final stages of disintegration by fibrocytes. There are no more polymorphs visible. Foreign body cells are not found.

FIG. 4.—Appearance of a bone-gap filled with alginate at four weeks. There are only minute traces of CaAlg at the margins of the line of junction. Bone and site of union look normal.

FIG. 5.—Control at three days. The transverse section of the femur (guinea-pig) is shown at three days. Muscle, bluntly dissected, was allowed to fall back in place. An area of hemorrhage and a massive polymorphonuclear reaction is seen.

FIG. 1



Sections fixed in alcohol and stained with hematoxylin-eosin, and in some cases with indigo-carmin, showed a progressive absorption of the amorphous clot by phagocytosis. Figure 2 shows the appearances of remains of a clot seven days after injection. The clot shows up as a slightly basophilic amorphous mass, broken up into fragments, and the margins are invaded by polymorphonuclear leukocytes. There is a marked polymorphonuclear leukocytosis around the area, denoting an aseptic inflammatory process. No foreign body giant cells are visible. At 14 days (Fig. 3) leukocytosis has subsided. There is massive fibrous tissue invasion of the remaining fragments of the clots, while some parts of it are already replaced by fibrous tissue. No foreign body giant cells are visible in the section.

In another series of rabbits, clots were prepared *in situ* in sites prepared in the radius of the animal. The rabbits were anesthetized by intraperitoneal nembutal. The foreleg was shaved and incised over the shaft of the radius. A length of 2-3 mm. was sawed out of the shaft of the bone, and the clot was inserted *in situ* by dropping a few drops of 5 per cent sodium alginate into this bed, followed immediately by calcium chloride drops over it. The clot was at once seen to contract and it was then gently moulded into the bone-gap. Fascia and skin were then sutured with silk. In some animals, the strength of the clot was altered by using a 3 per cent solution of sodium alginate and drops of 0.5 per cent calcium chloride, in order to compare the respective rates of absorption.

The animals were killed two and four weeks after the operation, and the bone was removed for decalcification, fixation, staining and serial section. The paraffin wax method was used after decalcification.

Figure 4 shows an alginate clot-filled bone-gap four weeks after the operation. Only minute traces of the clot are visible; the gap is filled with new bone, and the bone looks normal.

In bone-gaps filled with the weaker concentration of clot (3 per cent NaAlg and 0.5 per cent CaCl_2), the appearances are at two weeks similar to those seen in Figure 4, at four weeks, after the insertion of a 5 per cent sodium alginate and 2 per cent calcium chloride clot.

FIG. 6.—Control at seven days. The hemorrhagic area is decreasing. Fibroblasts are seen to replace the early polymorphs. Repair is in progress.

FIG. 7.—Calcium alginate film around femoral shaft at three days. Areas of hemorrhage are seen around the film. Massive polymorphonuclear reaction is seen.

FIG. 8.—Calcium alginate film around femoral shaft (guinea-pig) at seven days. The bone shows periosteal proliferation. Only a thin trace of film is visible in one area. Fibroblasts and a few macrophages are seen. Repair is in progress.

FIG. 9.—Scleral wound in the eye of a rabbit at seven days. There is only a thin roof of conjunctiva over the gap which is not yet healed (control.)

FIG. 10.—Scleral wound in the eye of a rabbit at seven days. Treated with calcium alginate film placed between conjunctiva and sclera. The wound is completely healed. The film is still visible as a thickening of the wound site. It is invaded by fibroblasts and is being replaced by tissue.

FIG. 11.—Burn (rabbit) at three days. The burnt area shows necrosis of the epidermis and disappearance of the hair follicles.

ALGinate PRODUCTS IN SURGERY

Fig. 7



Fig. 9



Fig. 6

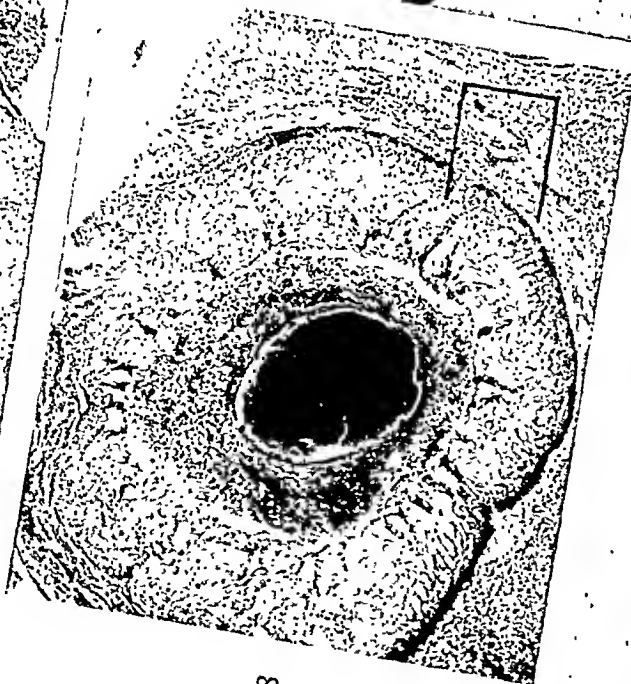


Fig. 8



Fig. 10

(2) *Calcium Alginate Film in Tissue*: Three series of experiments were carried out with films. Rabbits and guinea-pigs were used.

In the first series films of 80 μ thick calcium alginate was introduced around the femoral shaft of the guinea-pig, from which the muscle was detached by blunt dissection. The other femoral shaft was used as a control, using no material to wrap round the bone; the muscle was detached by blunt dissection and was allowed to fall back into place. The wounds were closed with silk sutures, and the animals were sacrificed at periods of 3-7-14 days after the operation. The bone and the surrounding muscle were removed *en bloc* for section. Intraperitoneal nembutal was the anesthetic in all operations.

Figures 5, 6, 7 and 8 show the respective appearances of some of the specimens. In the controls, a marked aseptic inflammation (polymorphonuclear leukocytosis) is visible at three days. At seven days the inflammation has subsided and fibroblasts appear. The bone is reacting with a new layer of periosteal bone.

In the sections showing the appearances of the femoral shafts around which calcium alginate films were wrapped, the reaction is much the same. Around the edges of the film there is a marked hemorrhagic and polymorphonuclear reaction at three days; at seven days there is normal progress of repair with invasion of lymphocytes and fibroblasts. There are a few macrophages in the section. At 14 days a trace of the calcium alginate film only is detectable. The area occupied by it is replaced by fibrous granulation tissue and the bone shows signs of periosteal activity.

In the second series of animals calcium alginate film was introduced into traumatized muscle. After intraperitoneal anesthesia by nembutal the rectus abdominis was opened through a paramedian incision, and was traumatized by blunt dissection. A postage stamp-sized film was introduced into the site thus prepared. To facilitate the removal of the biopsy specimen a green nylon suture was inserted near the site. Biopsy four weeks after insertion of the film showed complete absorption of the film and only a small fibrous cicatrix amidst healthy muscle bundles was visible at the site of insertion.

In the third series (reported on fully elsewhere¹³), rabbits were used; and calcium alginate film was introduced in the cocaine-anesthetized eye of the animal, between the conjunctiva and the sclera, in the region of the limbus. The object of this experiment was to demonstrate the tissue reaction and tissue isolating behavior of calcium alginate and to find out whether it was of use in the prevention of vitreous prolapse through incised wounds of the sclera.

Figures 9 and 10 show sections through the eyes of two rabbits; in one a calcium alginate film was inserted between the conjunctiva and sclera; in the other, section of a control eye is shown. Both specimens are from eyes one week after operation.

The control section shows a marked gap in the sclera, which is notoriously slow in healing; only a thin roof of conjunctival tissue has reformed. In the treated eye, the gap in the sclera is completely bridged by fibrous tissue with

elements of true scleral fibers; the calcium alginate film is shown invaded by fibroblasts, and is in the process of final fragmentation. There were no conjunctivoscleral adhesions.

(3) *Local Clotting of Alginate (and Alginate Plasma) on Burns*: In this series burns were produced on the shaved backs of rabbits with electrocautery, after preliminary intraperitoneal nembutal anesthesia. Two burns were created on each animal; on the one side, a clot of calcium alginate, or calcium alginate with plasma, was produced; on the control side the burn was treated with a saline wash followed by triple-dye paint. Between the infliction of the burn and the start of the treatment five-minute intervals were kept. The method of producing the alginate or alginate plasma clot was as follows: One drop of 5 per cent sodium alginate (with or without plasma) was allowed to spread on the burn; one drop of 2 per cent calcium chloride solution was added to the spread out film, producing the clot immediately. The animals were sacrificed at three and seven days, respectively, after the infliction of the

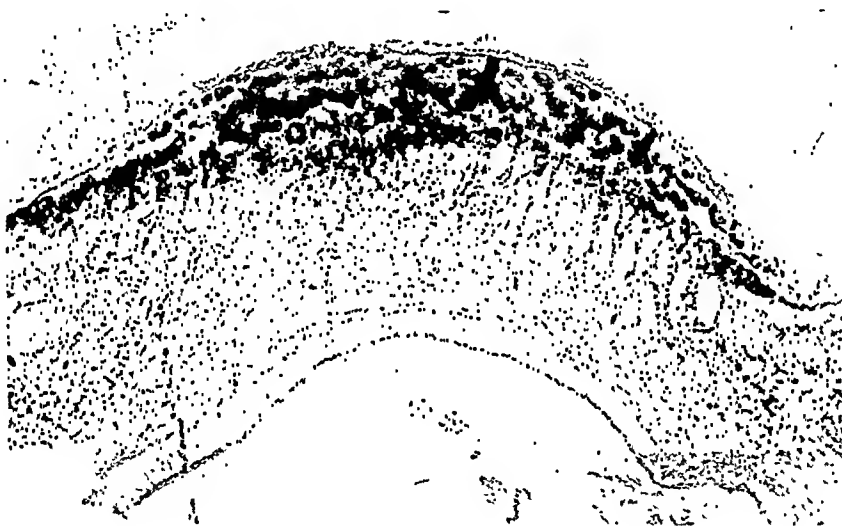


FIG. 12.—Burn (rabbit) treated with calcium alginate clot at three days. A thin surface of epidermis is necrosed and débris are incorporated in the clot. The underlying tissue is edematous, hair follicles are present and degeneration is far less advanced than in Figure 11.

trauma. The area of the burns was removed and submitted for serial sectioning.

Figures 11 and 12 show the appearances three days after the burn. In the control animals, the whole area of the burnt epidermis presents as necrosed tissue. All hair follicles have disappeared from this area (Fig. 11).

In the burn treated with calcium alginate, the appearances are vastly different. A thin surface layer of the epidermis is necrosed and mixed up with parts of the film which seems to have taken up the necrotic débris in its substance. The underlying tissue shows a fair degree of edema, but degeneration has not taken place to the extent it has in the control burn. Some hair follicles remain and look normal.

FIG. 13-A



FIG. 13-B

FIG. 13.—A and B.—Liver (cat) six weeks after resection of oval area from liver substance. The liver looks normal. At the wound site many alginate gauze shreds are visible. These shreds are in process of absorption and numerous fibroblasts and a few foreign body giant cells are visible.

In the animal burns examined seven days after infliction of the thermal trauma the appearances are again in marked contrast. The triple-dye treated side is necrosed, there is some fibroblastic reaction from the periphery; hair follicles are absent. In the alginate-treated side the regeneration of tissue is more marked, some hair follicles are present and appear normal. Almost identical findings were made in the cases treated with the alginate-plasma clots.

(4) *Calcium Alginate Gauze in Capillary Hemorrhage:* In this series of experiments cats were used. After intravenous nembutal anesthesia a high paramedian incision was made to the right of the midline. The left lobe of the liver was pulled out of the wound by traction, and a deep oval area was resected

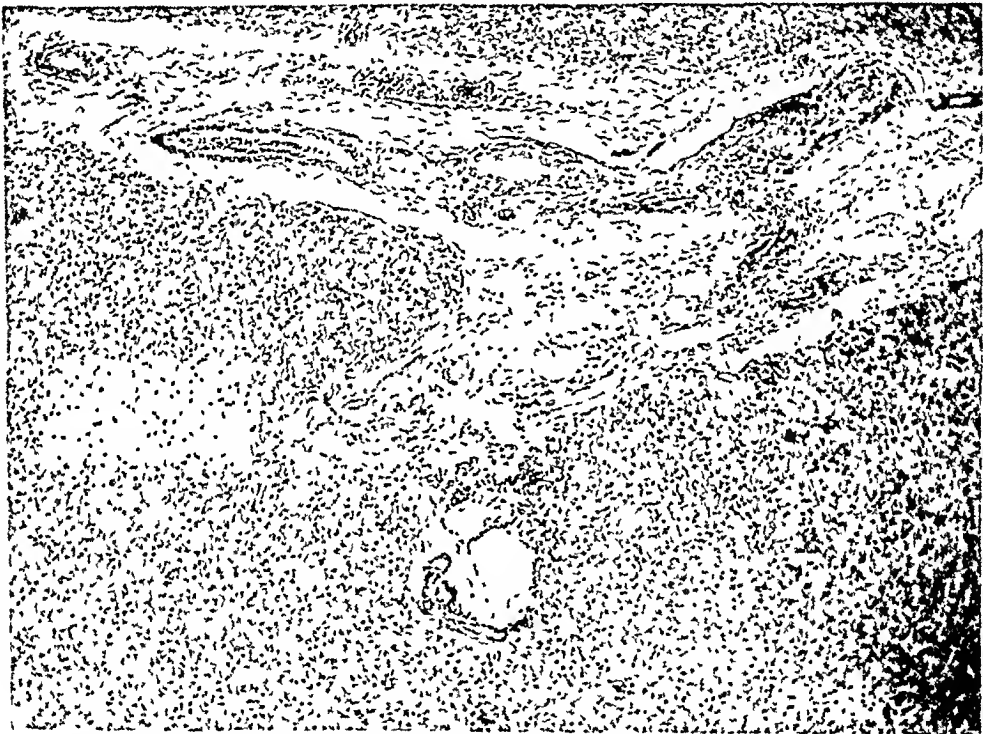


FIG. 13-C.—Section from liver of cat (Figs. 13-A and 13-B) showing alginate gauze shreds in course of disintegration. Fibrocytic reaction around shreds of material. Surrounding liver normal.

from the organ. There was immediate copious hemorrhage from this area, into which calcium alginate gauze was packed, under slight pressure. No sutures were inserted to anchor the gauze which became quickly clotted to the surrounding area.

The cats were kept alive for six weeks. After the first few days during which they were restless and did not touch their food, and had no bowel or bladder action, their appetite returned, defecation and micturition became normal. Recovery was uneventful, and at the time of sacrificing the animals for section they were in good health.

The microscopic appearances of these liver sections was in conformity with the previously reported observations on the behavior of calcium alginate in

tissue. Shreds of the material appear as profuse hyaline masses, all of which appear to be in a process of digestion by phagocytic action. Numerous fibroblasts and some foreign body giant cells are present. The surrounding area of the liver shows normal granulation tissue. Some muscle bundles, involved in the section, are being replaced by fibrous tissue (Fig. 12). In other sections there are traces of more marked hemorrhages in the liver. The area around these clots looks normal. Inflammatory cells are still present at the periphery of the hemorrhages and scanty shreds of alginate gauze surrounded and being digested by phagocytes can be identified.

In all the six cases of experimental hepatic hemorrhage the massive bleeding was promptly controlled by packing the oozing area with the alginate gauze.

From the foregoing experiments on alginate products, it becomes clear that this substance, used as a clot, film or gauze, is absorbed in animal tissues. Tissue reaction to it is minimal; its rate of absorption can be varied by using various strengths of sodium alginate or calcium chloride. The absorption rate, naturally, further depends on the physical form and bulk of the product. Thus, alginate cloth or gauze is slowest, and thin alginate film quickest in absorption in living tissue.

Preliminary bacteriostatic experiments have further shown that alginate products are readily sterilizable by autoclaving; preliminary experiments (not yet reported on) with penicillin have established that alginate products had no inhibitory action on penicillin.

It is hoped that this report on the possible uses of alginates in surgery will awaken further interest. Exigencies of the service in war-time have made it impossible to conduct a more complete examination of the many problems at issue. It has been shown, however, that alginates possess certain properties which make their surgical use attractive.

I wish to express my thanks to Lieut. General Sir Alexander Hood, Director-General, Army Medical Services, for permission to publish this paper.

REFERENCES

- ¹ Ferry H., and Morrison, P. F.: *J. Clin. Investigation*, 23, 566-572, July, 1944.
- ² Bailey, O. T., Hawn, C. Z., and Ford R.: Report to the Proctor Fund, 1943.
- ³ Ingraham, F. D., and Bailey, O. T.: *J. Clin. Investigation*, 23, 591-596, July, 1944.
- ⁴ Frantz, V. K.: *ANNALS OF SURGERY*, 118, 116-126, July, 1943.
- ⁵ Putnam, T. J.: *ANNALS OF SURGERY*, 118, 127-129, July, 1943.
- ⁶ Frantz, V. K., Clarke, H. T., and Lattes, R.: *ANNALS OF SURGERY*, 120, 181-198, August, 1944.
- ⁷ Curtis, R. H., and Brewer, J. H.: *Arch. Surg.*, 48, 130-136, February, 1944.
- ⁸ Stanford, E.: *Chem. News*, 47, 254, 1883.
- ⁹ Stanford, E.: *J. Soc. Chem. Ind.*, 3297, 1884.
- ¹⁰ Solandt, O. M.: *Quart. J. Exper. Physiol.*, 31, 25-30, July, 1941.
- ¹¹ Blum (Blaine) G.: *Lancet*, 2, 75-78, July, 1944.
- ¹² Gough, J.: Welsh National School of Medicine: Personal communication. August, 1945.
- ¹³ Blaine, G., Dollar, J. M., and Sorsby, A.: *Transactions of Ophth. Soc., U. K.*, 1945.
- ¹⁴ Frantz, V. K., and Lattes, R.: *J. A. M. A.*, 120, 798-801, November 17, 1945.

NUTRITIONAL REHABILITATION OF SURGICAL PATIENTS

JOHN H. REMINGTON, M.D.,
FELLOW IN SURGERY, MAYO FOUNDATION

J. ARNOLD BARGEN, M.D.,
DIVISION OF MEDICINE

AND

JOHN DEJ. PEMBERTON, M.D.,
DIVISION OF SURGERY
MAYO CLINIC

ROCHESTER, MINNESOTA

MANY RECENT ADVANCES in medicine can be attributed to a better understanding and application of the basic medical sciences. The needs of patients for fluids and electrolytes have been studied and determined by many investigators and the value of transfusions of blood and plasma now are well-recognized. Gastro-intestinal decompression, as well as chemotherapy, control of bleeding and clotting, and the newer products, such as penicillin, have all aided in better care of patients.

The nutritional state of the patient long has been recognized as an important factor in surgical risk and convalescence, but the importance of thorough understanding is only now beginning to be appreciated. Ravdin, and his associates,^{17, 22} as well as others,^{2, 9, 16} have called attention to the importance of adequate nutrition in surgical patients. Recently, Mulholland, and his coworkers^{4, 15} pointed out that the postoperative convalescence of patients who have undergone gastrectomy and who are fed by tube and maintained in positive nitrogen balance, was much shorter with an actual gain in weight compared to a control group of patients who had undergone gastrectomy and received the usual postoperative care. Madden and Clay¹⁰ have stated that high intake of protein compensates for increased catabolism resulting from injury to the body in experimental animals.

The need of a high protein diet in healing of wounds has been emphasized by Harvey and Howes.⁷ Postoperative separation of abdominal wounds still occurred in dogs when every other factor except hypoproteinemia was controlled in experiments carried out by Thompson, Ravdin, and Frank.²³ The protective action of a high protein diet against a virulent strain of pneumococci has been demonstrated in mice by Sako.²⁰ Also, the protective action of a high protein diet against necrosis of the liver which was produced by chloroform anesthesia was demonstrated by Davis and Whipple,⁵ in 1919, and more recently by Ravdin, and his group.⁶

Now that the importance of ingestion of protein is becoming more apparent, emphasis must be placed on the quality of protein¹¹ and its amino-acid content, as well as on the quantity of protein.¹⁹ Miller, Ross and Whipple¹⁴ have shown that methionine is the one amino-acid which protects protein depleted animals against necrosis of the liver which is produced by chloroform anesthesia.

The importance of vitamins is beyond dispute, but they perhaps have been given too prominent a part in the nutritional management of surgical patients at the expense of other equally important factors. Vitamin C is known to be a determining factor in the tensile strength of wounds¹ as well as the maturation of precollagen fibers.⁸ However, there is evidence now that vitamin C is necessary for the complete metabolism of phenylalanine,²¹ one of the essential amino-acids. Whether proper healing of wounds is dependent on vitamin C or on the availability of the essential amino-acids is yet to be determined. Mulholland, and his coworkers,¹⁶ in an interesting report, pointed out the effect on healing of an adequate intake of nitrogen in a series of 35 cases of decubitus ulcers which had persisted in spite of high vitamin, high caloric diet.

Patients who require operation for recovery often can be prepared by simple means rather than denied operation because of severe nutritional deficiencies. The following case illustrates what can be done in a seemingly hopeless case:

Case Report.—The patient, a male, age 53, was admitted to the Mayo Clinic in a critical condition and was hospitalized immediately. He had been operated upon elsewhere for obstruction of the small intestine three weeks before his admission. An enterostomy had been performed at that time. The incision had separated a few days post-operatively, and a loop of bowel had protruded and had been incised. Hence, two enteric stomas between which there was a very short loop of jejunum were present.

On examination, the patient was severely dehydrated and emaciated, and the abdominal incision was widely separated and raw. The upper enteric stoma was evidently high in the jejunum, as food taken by mouth would appear on the abdomen a few minutes after ingestion.

The level of hemoglobin was 13.0 Gm. per 100 cc. of blood. Erythrocytes numbered 3,790,000; and leukocytes 12,000 per cubic millimeter of blood. The sedimentation rate (Westergren) was 98 mm. in the first hour. The level of urea in the blood was 20 mg. per 100 cc. Temperature was elevated slightly, 100° F., and the respiratory rate was 20 per minute. Urinalysis gave negative results. A roentgenogram of the abdomen showed a short distended loop of small intestine. Proctoscopic examination and roentgenologic examination of the colon, made some little time after admission, failed to reveal any intrinsic intestinal disease.

The patient was given 500 cc. of whole blood and fluids parenterally. Aluminum paste was applied to the skin around the wound and continuous suction was applied to the wound. He had been on a general diet before admission, but this was discontinued as the food quickly appeared on the skin of the abdominal wall. Even a glass of milk or water acted as a bolus of food and was expelled through the enteric stomas. Food, prepared after the manner of Spies, was administered by drip through a stomach tube and this also quickly appeared on the abdomen.

In an attempt to utilize the short loop of small intestine between the stomach and the upper enteric stoma it was thought best to give nourishment slowly by the drip method that could be absorbed immediately and did not have to be digested. Nine hundred cubic centimeters of a 20 per cent solution of amino-acids* in the form of an acid hydrolysate of casein was mixed with 2,000 cc. of 20 per cent solution of glucose. This solution which provided about 2,100 calories was given slowly by the continuous drip method through the nasal tube. The patient received daily 1,000 cc. of 5 per cent solution of glucose in distilled water intravenously and 1,000 cc. of saline solution to which was added 20 mg. of vitamin C and adequate vitamin B-complex. Although most of the food prepared by the Spies formula was expelled through the enteric stoma, about 1,000 cc. was given daily to provide additional calories.

* Supplied by Frederick Stearns & Company.

This program was continued for two months. The patient gradually emerged from what seemed a hopeless condition. At first considerable quantities of the mixture passed through the enteric stoma, but this soon decreased. The patient was allowed out of bed on the 27th day. He weighed 119 pounds (54.0 Kg.) on the 39th day and 125 pounds (56.7 Kg.) on the 59th day. Although it was impossible to weigh him on admission, he certainly did not weigh much more than 100 pounds (45.4 Kg.).

At operation, two months after admission, the loops of small intestine were found to be matted together so that it was impossible to explore the peritoneal cavity. A lateral jejunojejunostomy was established between two loops of intestine, one about 5 inches (12.7 cm.) proximal and the other 5 inches distal to the proximal enteric stoma. A pelvic abscess was drained also. After the operation it was estimated that the jejunojejunal anastomosis side-tracked about one-fourth of the fecal current, so that the diverted fourth came through the distal enteric stoma and about three fourths through the proximal enteric stoma.

Five months after this operation the patient weighed 160 pounds (72.6 Kg.). At this time he was operated upon again and it was possible to close both enteric stomas. He has remained well since that time.

Although nitrogen balance has been maintained in man for as long as 17 days by the intravenous administration of a mixture of glucose, amino-acids, and an emulsion of fat,³ the gastro-intestinal tract still remains the preferable route of alimentation of large amounts of nitrogen and nourishment. Most of the available preparations of amino-acids are made by the digestion of casein or fibrin and contain a high percentage of glutamic acid, the amino-acid which in recent toxicity studies¹³ has been shown to cause vomiting when it is administered intravenously. Furthermore, studies of nitrogen metabolism^{12, 18} have revealed that nitrogen administered orally in the form of amino-acids is utilized several times more effectively than when it is administered intravenously. The realization of the importance of nitrogen balance in preoperative, as well as in postoperative care, and the correction of serious imbalances will aid in lowering surgical mortality and morbidity.

REFERENCES

- ¹ Bourne, G. H.: Vitamin C and Repair of Injured Tissues. *Lancet*, 2, 661-664, December, 1942.
- ² Brunshwig, Alexander, Clark, D. E., and Corbin, Nancy: Postoperative Nitrogen Loss and Studies on Parenteral Nitrogen Nutrition by Means of Casein Digest. *ANNALS OF SURGERY*, 115, 1090-1105, June, 1942.
- ³ Clark, D. E., and Brunshwig, Alexander: Intravenous Nourishment with Protein Carbohydrate and Fat in Man. *Proc. Soc. Exper. Biol. & Med.*, 49, 329-332, March, 1942.
- ⁴ Co Tui, Wright, A. M., Mulholland, J. H., Carabba, V., Barcham, I., and Vinci, V. J.: Studies on Surgical Convalescence: I. Sources of Nitrogen Loss Postgastrectomy and Effect of High Amino-acid and High Caloric Intake on Convalescence. *ANNALS OF SURGERY*, 120, 99-122, July, 1944.
- ⁵ Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia—Paper I. *Arch. Int. Med.*, 23, 612-635, May, 1919.
- ⁶ Goldschmidt, Samuel, Vars, H. M., and Ravdin, I. S.: The Influence of the Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform, and the Probable Mechanism of their Action. *J. Clin. Investigation*, 18, 277-289, May, 1939.

- ⁷ Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound. *ANNALS OF SURGERY*, 91, 641-650, May, 1930.
- ⁸ Hunt, A. H.: The Rôle of Vitamin C in Wound Healing. *Brit. J. Surg.*, 28, 436-461, January, 1941.
- ⁹ Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema. *Arch. Surg.*, 27, 159-177, July, 1933.
- ¹⁰ Madden, S. C., and Clay, W. A.: Protein Metabolism and Protein Reserves during Acute Sterile Inflammation: High Protein Intake-Compensates for Increased Catabolism. *J. Exper. Med.*, 82, 65-76, July, 1945.
- ¹¹ Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization. *Physiol. Rev.*, 20, 194-217, April, 1940.
- ¹² Madden, S. C., Anderson, F. W., Donovan, J. C., and Whipple, G. H.: Plasma Protein Production Influenced by Amino-acid Mixtures and Lack of Essential Amino-acids: A Deficiency State Related to Unknown Factors. *J. Exper. Med.*, 82, 77-92, August, 1945.
- ¹³ Madden, S. C., Woods, R. R., Shull, F. W., Remington, J. H., and Whipple, G. H.: Tolerance to Amino-acid Mixtures and Casein Digests given Intravenously. *J. Exper. Med.*, 81, 439-447, May, 1945.
- ¹⁴ Miller, L. L., Ross, J. F., and Whipple, G. H.: Methionine and Cystine: Specific Protein Factors Preventing Chloroform Liver Injury in Protein-depleted Dogs. *Am. J. M. Sc.*, 200, 739-756, December, 1940.
- ¹⁵ Mulholland, J. H., Co Tui, Wright, A. M., and Vinci, V. J.: Nitrogen Metabolism, Caloric Intake and Weight Loss in Postoperative Convalescence: A Study of Eight Patients undergoing Partial Gastrectomy for Duodenal Ulcers. *ANNALS OF SURGERY*, 117, 512-534, April, 1943.
- ¹⁶ Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V. J., and Shafroff, B.: Protein Metabolism and Bedsores. *ANNALS OF SURGERY*, 118, 1015-1023, December, 1943.
- ¹⁷ Ravdin, I. S., Stengel, Alfred, Jr., and Prushankin, Mitchell: The Control of Hypoproteinemia in Surgical Patients. *J. A. M. A.*, 114, 107-111, January, 1940.
- ¹⁸ Remington, J. H.: Unpublished data.
- ¹⁹ Rose, W. C.: The Significance of the Amino-acids in Nutrition. *The Harvey Lectures*, s. 30, 1934-1935, pp. 49-65.
- ²⁰ Sako, W. S.: Resistance to Infection as Affected by Variations in the Proportions of Protein, Fat, and Carbohydrate in the Diet: An Experimental Study. *J. Pediat.*, 20, 475-483, April, 1942.
- ²¹ Sealock, R. R., and Silberstein, Hannah E.: The Control of Experimental Alcaptonuria by Means of Vitamin C. *Science*, n.s., 90, 517, December, 1939.
- ²² Stengel, Alfred, Jr., and Ravdin, I. S.: The Maintenance of Nutrition in Surgical Patients: With a Description of the Orojejunal Method of Feeding. *Surgery*, 6, 511-519, October, 1939.
- ²³ Thompson, W. D., Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption. *Arch. Surg.*, 36, 500-508, March, 1938.

A TECHNIC FOR TESTING HYPERTENSIVE PATIENTS PREOPERATIVELY*

JAMES L. SOUTHWORTH, M.D., AND HENRY I. RUSSEK, M.D.

BALTIMORE, MD.

STATEN ISLAND, N. Y.

U. S. MARINE HOSPITALS

SINCE 1930, numerous investigators have studied the cause or causes of hypertension, while surgeons have been interested in treatment by operations upon the nervous system. Allen and Adson,¹ Peet,² Grimson,³ and Smithwick⁴ have made contributions in this respect. At present, while students of the subject are still divided in opinion as to the advisability of surgical treatment, many surgeons now lean toward combined thoracolumbar sympathectomy as the best surgical therapy. Writers on this latter subject attest to the difficulty of properly selecting patients for operation; it is particularly difficult to predict accurately the result of operation insofar as lowering of blood pressure is concerned. Although improvement may follow sympathectomy with little or no significant lowering of pressure, it is generally agreed that it would be desirable to be able to predict this event preoperatively.

Recently, we reported our experiences with nerve blocking methods to predict the result to be expected from Smithwick's operation, insofar as lowering of arterial tension immediately postoperatively is concerned.⁵ In this report the technic of testing is more fully described. If further experience with this test substantiates its validity, it may be possible to determine preoperatively the extent of sympathectomy necessary to produce a satisfactory response.

Detailed discussion of the cause of essential hypertension is beyond the scope of this paper. It is sufficient to say that experimental work at present indicates a sequence of events as follows: Some unknown factor, probably psychic, initiates increased blood pressure, at first labile, which presumably arises from arteriolar vasoconstriction; as the disease progresses arteriolar sclerosis occurs, notably in the kidneys, and perpetuates hypertension, keeping it, also, more or less fixed. Quite likely, from experimental work, a renal pressor mechanism plays a prominent part in maintaining pressure — almost certainly in the phase of arteriolar sclerosis and possibly earlier. Just when it begins to play a part is not certain. In the later stages, readily demonstrable kidney and cardiac disease occurs. Malignant hypertension is probably an instance of the same condition accelerated.^{6, 7, 8}

Sympathectomy for treatment of essential hypertension is not supported by experimental evidence; this type surgery fails to prevent and does not reduce increased arterial pressure experimentally produced by Goldblatt's

* Published with permission the Surgeon-General of the United States Public Health Service.

method.⁷ Nevertheless, there is ample clinical evidence to support the belief that this type surgery, especially the Smithwick procedure, produces significant variation in the usual course of the disease. Even though hypertension may not be greatly reduced, regression in eyeground changes and particularly improvement in clinical symptoms have been observed many times. Symptomatic improvement may be explained away as a psychic effect, but regression of eyeground changes leads to the conclusion that the disease is modified. Final evaluation of results, however, awaits longer follow-up.

Granting that sympathectomy of the proper type in selected patients lowers blood pressure and produces profound changes and probably is of some curative value, by what mechanism does it produce its effects? How does it alter the mechanism of arterial tension? Some studies indicate that a change in renal hemodynamics occurs following operation, while others note no significant change in this respect. There is some evidence to indicate that the output of the heart is reduced with consequent reduction in pressure rather than any decrease in peripheral resistance. However, this concept fails to account for other changes produced by the operation. The answers to these questions likewise await the results of more study.

In an effort to duplicate the result of sympathectomy preoperatively, in order to study hypertension with pressure temporarily lowered, spinal anesthesia has been administered. Gregory, Lindley, and Levine⁹ studied a number of hypertensive patients before, during, and after spinal anesthesia, and concluded that, since most responded with a fall in blood pressure, spinal anesthesia releases peripheral vasoconstriction which is the cause of much essential hypertension. This concept has been criticized¹⁰ on the basis that vasodilatation produced by spinal anesthesia is postarteriolar rather than arteriolar, the seat of the underlying disturbance in hypertension. Page, and his coworkers, studying the effect of spinal anesthesia on hypertension, believe that patients fall into a neurogenic or humoral classification (although they believe that these are but two stages of the same condition) and that only neurogenic patients exhibit renal arteriolar vasodilatation under spinal anesthesia, with resulting blood pressure fall, and that such response, at least to a significant degree, does not develop in the humoral group (those with renal arteriolar sclerosis and self-sustained fixed hypertension).¹⁰ They suggest that such a test as this — high spinal anesthesia — might afford a basis for differentiating patients in the early or neurogenic phase of the disease from those in the later humoral phase and that, in so differentiating, a basis for selection for sympathectomy might be found.¹¹

Leaving aside the mechanism of action of spinal anesthesia in reducing the hypertension of some hypertensives, there are certain objections to its use for this purpose.

Spinal anesthesia produces a very profound effect; it reaches its height quickly and may overwhelm other blood pressure-compensating mechanisms, bringing about a quite precipitous fall. While this is not especially danger-

ous, it may mask the true picture. Likewise, it produces widespread muscular relaxation which may affect return of blood to the heart to a significant degree. Lastly, spinal anesthesia sufficiently high to mimic an extensive thoracolumbar sympathectomy is not without danger of undue cephalad spread and respiratory embarrassment or failure.

Previously, we have studied, for other reasons, the effects of peridural anesthesia on blood pressure in both normals and hypertensives. Using peridural anesthesia as a general term to include its common forms, caudal analgesia and segmented peridural block, the following facts may be noted:

Anesthetic solution deposited into the peridural space, either at its distal end by the caudal technic or in the lumbar or thoracic region by the segmental technic, diffuses in the peridural space—in the former technic upward and in the latter both cephalad and caudad. It runs always outside the duramater and cannot rise farther than the foramen magnum. The anesthetic solution never enters the subarachnoid space, never mixes with the spinal fluid, and never can enter the cranium. Rather, it diffuses out the intervertebral foramina and blocks the nerves at or close to this point. The sensory and autonomic nerves are blocked first; it has been shown that when there is loss of pain perception in a given segment with this type block there is sympathetic block in the same segment. The motor nerves are not usually much affected even in those blocks made for anesthetic purposes; and with proper concentration of solution, motor block may be almost completely eliminated. By means of amount of solution injected, force of injection, and control of position of the patient, a sensory and sympathetic block of almost any desired extent can be achieved by one or the other of these methods. In testing hypertensive patients, the sympathetic block is of more importance but the sensory block serves to mark the limits of effect.

The effect of this type anesthesia on normotensives depends upon the number of sympathetic segments anesthetized and the rapidity with which the block is brought about. In addition, there seems to be a critical level peculiar to each individual, varying from the ninth thoracic to the fourth thoracic segment, where a significant pressure drop occurs. Anesthetizing a greater number of segments tends to produce a greater fall in pressure. Rapidly extending anesthesia beyond the limits of the critical level produces a more precipitous and profound effect.

In studying essential hypertensives, effects similar to those in normotensives were noted, with the exception that in some hypertensives no drop at all could be produced. Otherwise, as just mentioned, rapidly ascending or spreading anesthesia produces a precipitous fall. This may be quite alarming to watch, but we have noted no ill effects from it. Presumably it is due to the same cause that produces so profound an effect in high spinal anesthesia (unsupported by pressor drugs); namely, overwhelming of other compensating mechanisms. Likewise, in hypertensives, as in normotensives, greater fall is produced by block of greater extent. In those hypertensives

who respond to this anesthesia with decreased tension, there seems also to be a critical level somewhere between the ninth and fourth thoracic segments at which a marked fall begins.

As has been described in more detail elsewhere,¹² in a group of 60 patients with essential hypertension, anesthesia varying from the tenth to the fourth thoracic segments produced a blood pressure fall to normal levels (below 140/90) in all but ten. These ten were not necessarily in the most malignant or advanced phases of hypertension, as judged by other clinical tests. An attempt to explain this fixation of pressure on the basis of the probable pathogenesis of hypertension would be conjecture at this time, but it seems reasonable to assume that, whatever the mechanism, it has reached an irreversible stage and presumably these patients would not be benefited by sympathetic surgery.

Aside from technical differences, the two methods of peridural anesthesia differ somewhat in their effects on the autonomic nervous system. Caudal analgesia, induced from the distal portion of the peridural space, blocks all the sacral segments—both somatic and autonomic—in addition to the lumbar and thoracic segments. Lumbar peridural anesthesia, on the other hand, may be adjusted to produce a block that quite closely approximates the Smithwick operation in extent of sympathetic denervation without producing any effect in the sacral segments. In a number of patients in whom both peridural and caudal blocks were performed, we have noted no differences in the effect on blood pressure. Presumably caudal analgesia produces vasodilatation in the pelvis which a well-adjusted peridural block does not; both produce vasodilatation in the lower extremities and in the thoracic area.

Quite empirically, we have used caudal analgesia and lumbar peridural anesthesia by the continuous technics to study patients with hypertension later operated upon by the Smithwick procedure. In a small group of patients there seems to be good correlation between these tests and the immediate postoperative recumbent blood pressure.¹²

TECHNIC OF CAUDAL ANALGESIA

Previous to administering caudal analgesia in the hypertensive, the status of kidney and cardiac function should be determined. Pressure should be reduced to as low a level as possible by medical regimen, such as rest and sedation. On the day of the test the patient may have a light meal; it is advisable to administer pentobarbital grains one and one-half an hour prior to the test. The anesthesia should be conducted in a quiet room by an operator in whom the patient has confidence. The blood pressure in one or both arms and in the lying position is noted.

A caudal needle is inserted into the sacral canal and attached to a reservoir of anesthetic solution. Care should be taken to avoid intravascular placement of the needle. We use metycaine 1 per cent or 1.5 per cent without addition of epinephrine. A test dose of 8 cc. of this solution is ad-

ministered and the effect observed for five minutes to determine that the needle has not been accidentally inserted into the subarachnoid space. If spinal anesthesia is not produced by this preliminary injection, 30 cc. of anesthetic solution is slowly given. The blood pressure is observed and recorded every 5 minutes. Thirty minutes after the injection of the initial dose, its maximum effect will have been achieved, usually to the tenth thoracic segment, as shown by testing the skin of the abdomen with a needle. Small patients, or the elderly, may require only 20 cc. as an initial dose.

If a higher level of anesthesia is desired at the end of the first period, a supplementary dose of 40 cc. of anesthetic solution is injected for the average patient. By this time, however, the operator will have a valuable guide to the individual response to this anesthetic procedure. If 30 cc. has produced effect well above the average, say to thoracic eight, he can assume that a second dose of 30 cc., rather than 40 cc., may be sufficient to raise the pressure to thoracic four or six, as height of effect in these doses is somewhat cumulative. On the other hand, if the original 30 cc. produces anesthesia to thoracic 12 only, it may be advisable to administer 50 cc. as the second dose to produce the desired level.

To determine the critical level at which a significant change occurs, blood pressure readings and skin testing should be performed every five minutes as the end-point may be quite sharp and might be missed during a longer interval.

In some patients we have found it necessary to administer as much as 40 cc. of solution every 20 to 30 minutes for three or four doses to produce a high level of skin anesthesia. If this amount is not effective it is our custom to discontinue caudal anesthesia and after a few days resume the test using the peridural technic outlined below.

In the average patient 70 cc. of anesthetic solution administered in two doses 30 minutes apart will produce anesthesia to thoracic six to four. To maintain this level for a time, further supplementary doses of 30 to 50 cc. every 45 minutes will be required according to the individual response of the patient. Should undue difficulty be experienced in raising the level of anesthesia, the table may be tilted to five-degree Trendelenburg position. Gravity will assist the solution in diffusing upward. If the anesthesia goes so high that a below-normal blood pressure is produced, cerebral anoxia may be prevented by elevation of the lower extremities on pillows. When the high level recedes, the test may then be continued, using smaller amounts of solution.

In using caudal analgesia for testing hypertensives, the general precautions and contraindications that apply to this method under other circumstances should be observed.^{13, 14} This technic should be avoided in the presence of infections of the skin, particularly if near the needle site. Deformity of the sacrum or obesity may render the technic difficult. We have avoided this test when there is evidence of coronary artery insufficiency.

TECHNIC OF LUMBAR PERIDURAL ANESTHESIA

Segmental block of the thoracic and upper lumbar somatic and sympathetic nerves can be achieved readily by lumbar peridural block since there is less space to be filled before reaching the desired nerves. Using Abajian's¹⁵ technic, which is essentially a single dose procedure, it is often possible to obtain quite accurately delimited anesthesia. For ease of control, however, we have preferred continuous lumbar peridural anesthesia when caudal block is not practicable.¹⁶ Using the continuous method, more accurate block can be achieved.

The patient is placed on a Lemmon continuous spinal mattress and the spine is flexed as for lumbar puncture. A malleable steel needle is inserted at the first or second lumbar interspace down into the interspinous ligaments. The stylet is then withdrawn and a 2 cc. syringe containing saline is attached to the syringe. The needle and syringe together are advanced through the ligaments. At the moment the point of the needle enters the peridural space the saline solution rushes in, pushing the dura forward. At this point progress of the needle is stopped. If no spinal fluid appears on aspiration, tubing to a reservoir bottle is attached to the needle, and the patient is turned to the recumbent position. Five cubic centimeters of 1.5 per cent metycaine solution are then injected and the effect observed for five minutes, an additional test to prevent intraspinal injection. If 5 cc. produces no demonstrable effect after five minutes, it is safe to proceed.

Twenty cubic centimeters of solution are injected for the initial dose, and skin anesthesia and blood pressure are determined every 5 to 15 minutes. At the end of 30 minutes, maximum effect of the initial dose will have resulted. Before injecting supplementary doses, the anesthetic status of the patient must be tested each time. Motor effects in the lower extremity are minimal or absent from these small doses peridurally. As an additional precaution before every injection, 5 cc. of 1.5 per cent metycaine solution are injected. If no widespread motor effects are observed after five minutes, the operator is assured that the needle has not shifted into the subarachnoid space. A supplementary injection of 15 to 30 cc. may be administered to extend or maintain the desired anesthesia.

The initial injection of 20 cc. of 1.5 per cent metycaine at the first lumbar interspace with the patient level usually produces a band of somatic and sympathetic anesthesia from T8 to L1 segments inclusive in the average adult male 30 minutes after injection. From this effect some fall in pressure is usually observed. A supplementary injection of 20 cc. 30 minutes after the initial injection reinforces the first anesthesia and usually extends it from T6 to L3 inclusive. As in caudal block, gravity may be used to influence spread of the anesthetic solution through manipulations of the table shortly after an injection.

From a theoretic standpoint at least, lumbar peridural anesthesia is a better test because of the reasons mentioned above. It more nearly repro-

duces the denervation achieved in thoracolumbar sympathectomy. We find it technically more difficult and for this reason employ high caudal block whenever possible.

SUMMARY

Experience with caudal and peridural anesthesia in hypertensive patients indicates that these technics may be used to predict the result of sympathectomy. The technic of application is described.

REFERENCES

- ¹ Allen, E. V., and Adson, A. W.: Physiologic Effects of Extensive Sympathectomy for Essential Hypertension: Further Observations. *Ann. Int. Med.*, **11**, 2151, 1938.
- ² Peet, M. M.: Splanchnic Section for Hypertension: A Preliminary Report. *Univ. Hosp. Bull., Ann Harbor, Mich.*, **1**, 17, 1935.
- ³ Grimson, K. S.: The Surgical Treatment of Hypertension: Collective Review. *Surg. Gynec., and Obst.*, **75**, 421, 1942.
- ⁴ Smithwick, R. H.: A Technic for Splanchnic Resection for Hypertension. *Surgery*, **8**, 1, 1940.
- ⁵ Russek, H. I., Southworth, J. L., and Zohman, B. L.: The Selection of Hypertensive Patients for Sympathectomy. *J.A.M.A.*, **128**, 1225, 1945.
- ⁶ Page, I. H., and Corcoran, A. C.: Arterial Hypertension: Its Diagnosis and Treatment. Chicago, Yearbook Publishers, 1945, Chap. 11.
- ⁷ Goldblatt, H., Kahn, J. R., and Lewis, H.: Studies on Experimental Hypertension: XVII Experimental Observations on Treatment. *J.A.M.A.*, **119**, 1192, 1942.
- ⁸ Castleman, B., and Smithwick, R. H.: Relation of Vascular Disease to Hypertensive State: Based on Study of Renal Biopsies from 100 Hypertensive Patients. *J.A.M.A.*, **121**, 1256, 1943.
- ⁹ Gregory, R., Lindley, E. L., and Levine, H.: Effects of Spinal Anesthesia on Blood Pressure of Hypertensive Patients: Possible Bearing on Pathogenesis of Essential Hypertension, *Texas Rep. Biol. and Med.*, **1**, 167, 1943.
- ¹⁰ Corcoran, A. C.: Comment on article of Gregory, *et al.*,⁹ *J.A.M.A.*, **123**, 1135, 1943.
- ¹¹ Page, I. H., Taylor, R. D., Corcoran, A. C., and Mueller, L.: Correlation of Clinical Types with Renal Function in Arterial Hypertension: II Effect of Spinal Anesthesia. *J.A.M.A.*, **124**, 736, 1944.
- ¹² Russek, H. I., Southworth, J. L., and Zohman, B. L.: *J.A.M.A.*, **130**, 927-929, 1946.
- ¹³ Hingson, R. A., and Southworth, J. L.: Continuous Caudal Anesthesia. *Am. J. Surg.*, **58**, 92, 1942.
- ¹⁴ Southworth, J. L., and Hingson, R. A.: Continuous Caudal Analgesia in Surgery. *ANNALS OF SURGERY*, **118**, 945, 1943.
- ¹⁵ Abajian, J.: Peridural Segmental Anesthesia with Intracaine. *Anesthesiology*, **4**, 372, 1943.
- ¹⁶ Hingson, R. A., and Southworth, J. L.: Continuous Peridural Anesthesia. *Anes. and Analg.*, **23**, 215, 1944.

UTILIZATION OF SKIN FROM DEFORMED AND USELESS FINGERS TO COVER DEFECTS IN THE HAND

EDWIN F. CAVE, M.D., AND CARTER R. ROWE, M.D.

BOSTON, MASS.

GUNSHOT WOUNDS of the hypothenar eminence of the hand, with or without fracture of the fifth metacarpal, frequently result in extensive scarring of the area and irreparable damage to the tendons, with resultant flexion contracture of the fifth finger, rendering it useless.

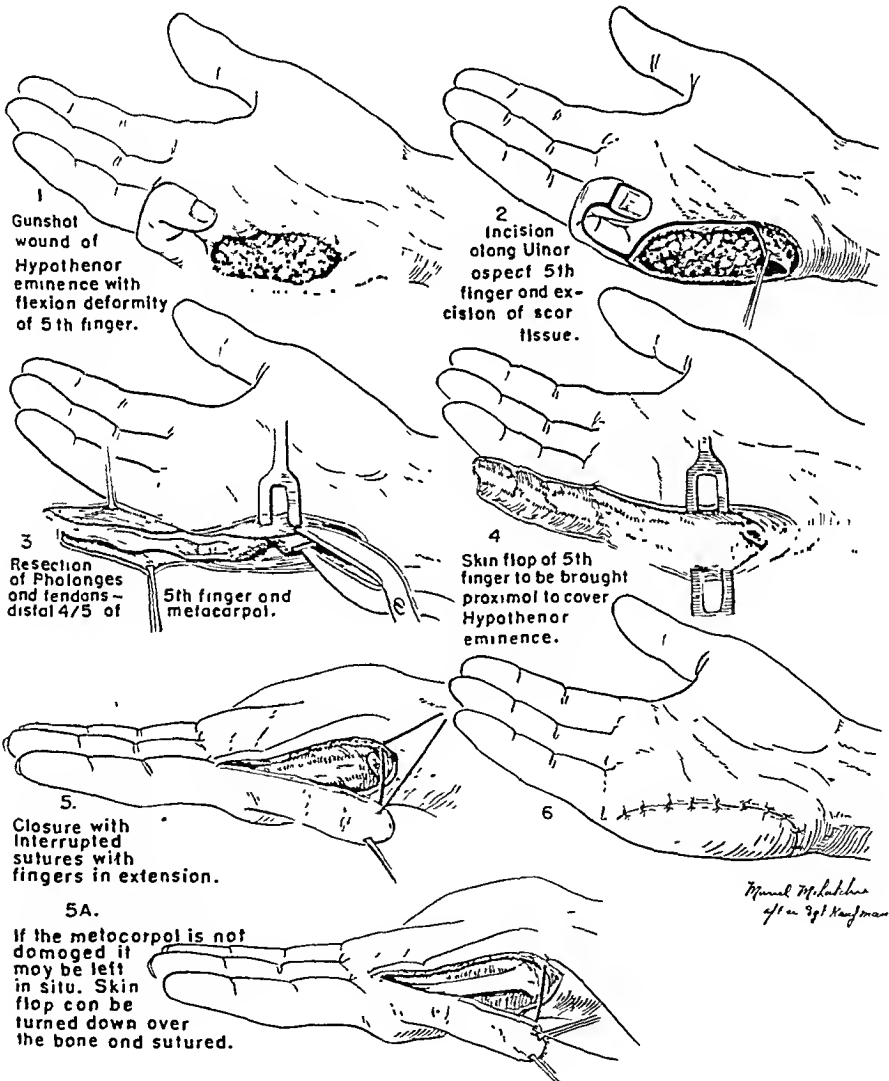


FIG. 1.—The above drawings illustrate the operative procedure for excision of scar and subcutaneous amputation of phalanges and metacarpal at the same time utilizing the skin flap to cover the defect created.

To correct this condition the following operative procedure has been used: (1) The incision circumscribes the nail and extends proximally along the ulnar aspect of the finger and around the margin of the scar. (2) The scar is excised completely down to the metacarpal. (3) If there has been extensive bone loss of the metacarpal, with nonunion, this bone is resected distal to its base. (4) The phalanges and tendons are removed subcutaneously. (5) The remaining skin flap, with its nerve and blood supply intact, is turned proximally to cover the skin defect. (6) As the flap is sewed with interrupted cotton or silk sutures, the remaining fingers are held in complete extension.

The value of this plastic procedure on the hand emphasizes the importance of preserving all possible skin of the hand at the time of the initial débridement when wounds of the hands have been sustained. The type of flap-graft described heals quickly and adjusts readily to its new location, because the circulation and nerve supply are preserved. The principles of this operation can be applied to cover any skin defect in the hand when it is associated with useless and deformed fingers.

The operation described was performed on five patients at the 105th General Hospital in the Pacific Theater. There was no difficulty in survival of the skin flaps. All grafts took readily, and the hands of all five patients were useful within two to three weeks after operation.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY

East Washington Square, Philadelphia, Pa.

BOOK REVIEWS

SCIENTIFIC MEDICAL AND TECHNICAL BOOKS PUBLISHED IN THE UNITED STATES OF AMERICA 1930-1944. Edited by R. R. Hawkins, National Research Council, Washington, D. C., 1946.

THIS IMPRESSIVE REFERENCE WORK of over eleven hundred pages was prepared under the direction of the National Research Council's Committee on Bibliography of American Scientific and Technical Books, and was edited by Mr. R. R. Hawkins, Chief of the Science and Technology Division of the New York Public Library. As its title implies, it comprises a selected list of scientific medical and technical books still in print, written by American authors, and published in the United States during the years 1930 to 1944, inclusive. It was the original intention of the Committee to include all important scientific and technical literature that met the requirements of nationality, date of publication and availability. However, to keep the work within practical limits, it was necessary to limit the field covered and the type of publication listed. Social sciences (economics, education and criminology) are excluded. The rest of the field of science is well covered. In the field of Technology, graphic arts—printing, photoengraving and allied subjects are omitted. High school and elementary textbooks are eliminated, and publications issued by states and territories with the exception of books from state university presses.

Selection of books for inclusion in this bibliography is based on works of merit currently in print and available for distribution in America and foreign countries, and represents publications one would expect to find on the shelves of a modern up-to-date library specializing in a given subject. It should be useful to librarians, professional and technical research workers, scholars and teachers in the fields covered.

This work lists about six thousand books, and describes them fully with complete titles, tables of contents, and descriptive rather than critical annotations. It includes kinds of illustrations, price, and size of book in height given in centimeters. The list is not intended to be a bibliography of best books, but is rather a descriptive compilation of important and useful publications in the various fields of science.

The arrangement of the work is well planned with table of contents, subject index, author index and directory of publishers. In order not to make it too voluminous to be practical, the Committee found it necessary to eliminate worth-while state government publications. To partially compensate for this, the editor includes a directory of state agencies in the United States issuing publications in geology, engineering and agriculture.

The typographical format of the work is an excellent example of modern printing art. Its style of arrangement and general make-up show unusual judgment and skill in the selection of type sizes and spacing, and aid the reader to find his information easily and quickly. At the same time, its unique design compresses a vast amount of important and condensed information on each page.

This publication is without doubt the most complete in its field. The majority of other similar works are little more than lists of authors and titles of publications, with almost no descriptions of contents of books listed. Never before has the field of American scientific and technical literature been so completely and accurately surveyed.

The work should prove an excellent means of furthering our cultural relations with other countries. The Department of State of the United States has made the first printing available as an official document for distribution in Central and South American countries. It is expected that later printings will also be available for the liberated countries of Europe and the Far East.

Books on scientific medicine, dentistry and closely related subjects are well covered and comprise over 300 pages of the text, or almost one-third of the work. Those on forensic medicine and the social aspects of medicine are eliminated together with publications on the costs of medical care and the socialization of medicine, even though there is extensive published literature on this subject.

This handy reference work is recommended to anyone having to do with the dissemination of scientific and technical knowledge in books, or about them—dealer, librarian, research worker or scholar.

WESLEY DRAPER.

ANNALS OF SURGERY

VOL. 125

FEBRUARY, 1947

No. 2



INTRODUCTORY REMARKS—FIRST CHURCHILL LECTURE

Eldridge Campbell, M.D., ALBANY, NEW YORK

DR. CHURCHILL, LADIES AND GENTLEMEN:

THE FIGHTING HAS CEASED, the contending nations are licking their wounds and may now reckon their gains and losses. No country ever really wins in a war; one side simply loses more than the other. Medicine's part in the victory was bought at the price of serious dislocation both of graduate and undergraduate education.

Fortunately, there were valuable gains as well. Under the stimulus of war, far-reaching advances came in the fields of chemotherapy, preventive medicine, and above all in surgery. These were made possible by men whose devotion to their profession was such that they could serve their goddess despite the handicaps of personal discomfort, of makeshift temples, and of the petty annoyances of an *ersatz* officialdom which often appeared more interested in the stroma than the parenchyma.

Thus, it was but natural that a group of friends of long association in the Mediterranean Theater should found a lecture in honor of Doctor Churchill, whose devotion to surgery, as well as to those practicing it, whose wisdom and openmindedness made him the Paré of World War II. To this end we have secured the willing services of a distinguished American scientist, Dr. Alfred Blalock, Professor of Surgery at the Johns Hopkins Medical School, who will deliver the first Edward D. Churchill Lecture: Doctor Blalock.

THE USE OF SHUNT OR BY-PASS OPERATIONS IN THE TREATMENT OF CERTAIN CIRCULATORY DISORDERS, INCLUDING PORTAL HYPERTENSION AND PULMONIC STENOSIS*

ALFRED BLALOCK, M.D.

BALTIMORE, MD.

FROM THE DEPARTMENT OF SURGERY OF THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL, BALTIMORE, MD.

THE SURGEON with a profound interest in the physiopathology of disease is to a large extent a product of the period in which we are living. The man in whose honor this lectureship is named is one of the most ardent advocates of the physiologic approach to surgery. Dating from the time when he worked with Doctor Drinker, and others, Doctor Churchill has continued his own investigations and has fostered research among his associates and pupils. In addition, Doctor Churchill has shown an admirable combination of attributes as an excellent clinical surgeon, a great professor of surgery, a successful

* The first E. D. Churchill Lecture, delivered at Boston, Massachusetts, before the Excelsior Surgical Club, and Guests, October 25, 1946.

military surgical consultant, and a surgical philosopher. In this, the first Churchill lecture, it is with a feeling of gratification that I discuss certain abnormalities of the circulation in the solution of which the physiologic approach is proving useful. I wish that the subject were broad enough to embrace more of the interests of your honored member.

In the past, the major emphasis in surgery has been concentrated on the removal of diseased tissues or abnormal growths. Better means by which various structures may be removed will be developed, but the scope of surgery by extirpation cannot be extended greatly since the field has been covered rather completely. The operative procedures under consideration in this lecture are not concerned with extirpation but rather with improving the function of organs which are left *in situ*. It is to be hoped that the problems connected with the transplantation of tissues from one subject to another will be solved ultimately and that diseased organs may be replaced by normal ones. In the meantime, it appears that a good deal can be accomplished from the viewpoint of improving the function of structures that cannot be dispensed with or replaced.

Turning our attention more specifically to the circulatory system, we see how remarkably effective nature is in dealing with many of the congenital and acquired abnormalities. For example, survival is possible following occlusion of some of the larger arteries of the body provided the occlusion is gradual rather than sudden and that there is not generalized arterial disease. Owings¹ has demonstrated experimentally that it is possible to perform successful complete occlusion of the thoracic aorta in multiple-stage operations. Clinical case reports show that life is possible in the presence of complete closure of the three major coronary arteries or in congenital atresia of the thoracic aorta or main pulmonary artery. It has been demonstrated experimentally that the portal vein may be occluded by multiple-stage procedures without causing death, and that, in man, gradual closure of the portal vein may take place without a fatal result. The spontaneous development of large collateral pathways following the occlusion of arteries or veins is one of the best defense mechanisms of the body against disease and injury. Unfortunately, the collateral circulation is not always sufficient to maintain the life of the individual or the part. More often the part does not function normally even though death or gangrene does not occur. Under these circumstances, certain well-known surgical measures may be of aid. I refer in particular to the use of sympathectomy in various vascular disorders. Reference should also be made to attempts to increase the collateral blood supply to ischemic tissues by causing the part to adhere to neighboring structures, as in the Beck² procedure.

This lecture, however, will not deal with these measures but rather with those in which the course and function of large arteries or veins are altered in such manner that they will deliver blood to, or drain blood from, an area other than that which they previously served. The procedures represent an attempt to increase arterial circulation to areas or venous drainage from areas beyond that which is possible through the development of normally-occurring collateral

pathways. Major attention will be devoted to portal hypertension on the venous side and to pulmonic stenosis on the arterial side. In addition, a few of the other conditions in which the principle may be utilized will be discussed briefly.

Before beginning a consideration of individual disorders, a few general remarks concerning blood vessel anastomosis may be in order. Naturally, the most important point is that the anastomosis shall remain patent. This is dependent to a considerable extent upon the caliber of the vessels that are used and upon the expertness with which the anastomosis is performed. Also, of great importance is the difference in the pressures on the two sides of the anastomosis. Other factors being equal, those anastomoses are most apt to remain patent in which there is the greatest difference in pressure on the two sides of the union. If the pressures on the two sides are approximately the same, the vessel with a high pressure and a pulsating flow is more apt to remain patent than the one with a low pressure and a nonpulsating flow. The statement which I am about to make has not been confirmed by adequate experimental observations, but it is probable that an anastomosis of a systemic artery to a vein would be most likely to remain patent, that an anastomosis of a systemic artery to a pulmonary artery would rank next, that an anastomosis of an artery to another systemic artery would rank third, and that a vein-to-vein anastomosis would be least apt to remain open. As stated previously, other factors, including the caliber and length of the vessels, the site of the operation, and the care with which the anastomosis is performed, influence the incidence of thrombosis.

The question arises whether blood vessel anastomoses are performed best by suture methods or by nonsuture methods³ in which material such as vitallium or tantalum is employed. Dr. T. N. P. Johns⁴ and I found that a vein-to-vein anastomosis is more apt to remain patent when the suture method is used as compared with the nonsuture method employing the vitallium tube. This result would be expected, in view of the fact that it is preferable to leave as little foreign material as possible in the region of the anastomosis. When a gap has to be bridged it may be necessary to use some method other than direct suture, but this is not the procedure of choice under the usual circumstances.

A point in technic in the anastomosis of large arteries, such as the aorta, is concerned with the decision whether the suture should include the entire thickness of the wall of the vessel or whether one should attempt a so-called anatomic approximation of the different layers. This point was discussed recently by Doctor Crafoord and Doctor Gross⁵ in relation to methods for uniting the ends of the aorta after the excision of a stenotic area. I agree with Doctor Gross that the suture should be an everting one and should include the entire thickness of the wall of the aorta. Further experimental work on this subject is needed. The problem does not arise in connection with the anastomosis of veins or of the smaller arteries in which the thin vessel wall will not permit an anatomic approximation of the different layers.

Another point which arises in connection with some of the operations is concerned with the performance of an end-to-end or an end-to-side or a side-to-

side anastomosis. In many cases only an end-to-end suture is feasible, but in others one of the other methods may be chosen. For example, in a splenorenal vein anastomosis one may unite the end of the splenic vein to the end of the renal vein after having removed the left kidney or may suture the end of the splenic vein to the side of the renal vein without doing a nephrectomy. Obviously, one advantage of the latter method is that the patient retains both kidneys. Some experimental work, which Doctor Johns⁴ and I performed recently, indicates that there is an additional advantage to the end-to-side anastomosis, in that thrombosis is less likely to take place. It was found that 90 per cent of the splenorenal anastomoses remained patent when the end-to-side method was used, whereas only 73 per cent of the end-to-end anastomoses remained open. It is likely that the large venous return from the kidney aids in maintaining patency of the anastomosis in the end-to-side type. The problem arises in portacaval anastomoses whether one should suture the end of the divided portal vein to the side of the inferior vena cava or should perform a side-to-side suture. The latter method is more difficult to perform and the opening is less likely to remain patent. In the anastomosis of a systemic to a pulmonary artery which is to be discussed subsequently, the end-to-side union is preferable in that it allows the diverted arterial stream of blood to flow to both lungs. Thus, it is apparent that an end-to-side anastomosis is in some instances preferable to an end-to-end one.

Attention will now be directed to those abnormalities in which a by-pass or shunt operation should be considered. The first condition to be discussed is hypertension of the portal vein or its tributaries.

PORTAL HYPERTENSION

In a consideration of portal hypertension it should be remembered that the portal venous system is interposed between two capillary beds. The portal vein normally receives the venous drainage from the gastro-intestinal tract, the pancreas, the gallbladder, and the venous sinuses of the spleen. Patients with portal hypertension may be divided into those with intrahepatic block and those with extrahepatic block. Although it is not possible always to be sure as to the nature of the block, much information can be gained from certain observations. It is usually possible to predict, on the basis of studies of liver function, whether the hypertension is due to portal cirrhosis or to extrahepatic blockage of part, or all, of the portal bed. A patient with splenomegaly, bleeding from the intestinal tract, anemia, leukopenia, thrombocytopenia, and normal liver function tests most likely has extrahepatic portal bed block. A history of antecedent pancreatitis or severe trauma to the epigastrium suggests the possibility of thrombosis of the splenic vein. In the absence of a history of abdominal trauma, the young child with an enlarged spleen, repeated hematemeses, and normal liver function tests may have occlusion of the portal vein as a result of continuation of the obliterative process in the umbilical vein and ductus venosus. Abnormal liver function tests indicate an intrahepatic obstruction. Whipple⁶ states: "If there is a high retention of bromsulphalein in the

blood 30 minutes after the intravenous injection, if the hippuric acid test is positive, if there is a reversal of the albumin-globulin ratio or if the cephalin flocculation test is positive, the presence of a cirrhosis with intrahepatic portal block is fairly certain. On the other hand, if these tests are negative it is safe to assume that the block is extrahepatic." It is obvious that patients with cirrhosis without portal hypertension do not fall within the scope of this lecture.

One of the difficulties in determining the site of extrahepatic blockage associated with hematemesis arises because of the variability in the point of entrance of the coronary veins. In some instances the coronary vein of the stomach enters the splenic vein, whereas in others it enters the portal vein. Rousselot⁷ has shown that esophageal varices do not usually occur in the presence of thrombosis of the splenic vein when the coronary vein enters the portal vein. Under such circumstances, splenectomy in the treatment of congestive splenomegaly is indicated. On the other hand, if there are esophageal varices and splenic vein thrombosis and if the thrombosis is proximal to the entrance of the coronary vein, splenectomy should be performed only if a splenorenal vein anastomosis is performed at the same time. It is usually difficult to determine the site of extrahepatic venous thrombosis. Venous pressure readings and venograms give valuable aid. Blakemore and Lord⁸ state that a venous pressure reading higher than 110 mm. of water should be considered abnormal. They advise the following course: "At the outset, a pressure reading should be taken from a branch of the superior mesenteric vein; if this is elevated, it may be taken as evidence of a block in the superior mesenteric vein, portal vein or intrahepatic portal block. A normal reading from a branch of the superior mesenteric vein and an elevated reading from a branch of the coronary vein of the stomach would indicate a block in the splenic vein, and, furthermore, strongly suggest that the coronary vein originates from the splenic vein distal to the site of obstruction. This evidence alone would make us favor performing a splenectomy followed by a splenorenal anastomosis rather than a splenectomy alone. In a case of congestive splenomegaly in which the superior mesenteric pressure is normal, the splenic vein pressure elevated but the coronary vein pressure approximately normal, we would be inclined to perform a splenectomy only." It is only fair to state that it is at times very difficult to determine accurately the venous pressure in these locations.

A difficult problem is presented by the patient with portal thrombosis and cavernomatous transformation of the portal vein. Under such circumstances the splenorenal vein anastomosis is probably the procedure of choice.

It is to be hoped that recent advances in the treatment of cirrhosis by the use of high protein-carbohydrate diet and high vitamin therapy will reduce the number of patients in whom some form of surgical therapy is considered necessary. On the other hand, it seems likely that many patients will develop portal hypertension and bleeding from the esophagogastro-intestinal tract. The problem of repeated bleeding is a particularly difficult one. My experience with the ligation of tributaries to esophageal varices has been very discouraging. The results of attempts to inject and coagulate varices leave much to be

desired, and the Talma-Morison omentopexy rarely results in improvement. The most physiologic method of surgical treatment is that in which an attempt is made to anastomose the portal and the caval circulations. The experience thus far with this method will be related briefly.

✓ In 1877, Eck,⁹ a Russian physiologist, developed the operation whereby a fistula between the portal vein and the inferior vena cava is made in order that he might carry out experimental studies of diseases of the liver and the relations of the liver to metabolism. He suggested that an anastomosis between the two veins might be used to sidetrack the venous return in obstruction of the portal vein. Quievolo,¹⁰ in 1893, everted the divided distal end of the portal vein over a glass tube and connected this to an opening in the inferior vena cava. Some of the animals lived for a period of months. The Eck fistula procedure was attempted in patients by several surgeons in 1910, and shortly thereafter. Probably the most encouraging result was that of Rosenstein,¹¹ who created an Eck fistula in an elderly woman with cirrhosis. This patient was strikingly improved at the time of the report five months after the operation. The high mortality rate associated with the operation discouraged its use, and it is only recently that the employment of this procedure in patients has been revived.

The recent interest in portacaval shunts has resulted to a considerable extent from the nonsuture method for blood vessel anastomosis devised by Blakemore and Lord.³ Whether or not one agrees with them that this method is preferable to a suture anastomosis, it is certain that it stimulated Whipple and Blakemore to the further use of the principle of the Eck fistula in the treatment of patients with intra- and extrahepatic block. At the time of their last report^{12, 13} (February, 1946), 14 patients had been operated upon. In four of these patients the site of the portal bed obstruction was extrahepatic and in the remaining ten it was intrahepatic due to portal cirrhosis. A splenorenal vein anastomosis was performed in some of the cases and a portacaval shunt in others. There were only two early postoperative deaths, and the majority of the surviving patients were improved. When there is freedom of choice, Blakemore¹³ is of the opinion that the portacaval shunt (anastomosis of divided distal end of the portal vein to the side of inferior vena cava) is preferable to the splenorenal anastomosis.

My own experience with this type of anastomosis is less extensive than that of Whipple and Blakemore, and the results are not so good as theirs. I think, however, that the procedure is a sound one. ✓ Because of the high portal pressure, the opening is more apt to remain patent than is the usual vein-to-vein anastomosis. There are several impressions which I have gained as a result of my experience: (1) Anastomosis of the portal vein and inferior vena cava is preferable when indicated to a splenorenal union in that it will conduct more blood and is more apt to remain patent; (2) if a splenorenal anastomosis is performed, suture of the proximal end of the splenic vein to the side of the renal vein is preferable to an end-to-end anastomosis; (3) suture of the divided distal end of the portal vein to the side of the inferior vena cava is preferable to

a side-to-side anastomosis since the opening is more apt to remain patent; and (4) it is not necessary to occlude the inferior vena cava completely while performing a portacaval shunt.

The foregoing remarks support the statement that portacaval shunt operations are still in the experimental stage and much remains to be learned about the choice of patients for operation and the choice of operative procedure. Despite the incompleteness of our knowledge, it does appear that the principle of portacaval shunts in the treatment of ascites and gastro-intestinal bleeding is a much sounder one than those previously advocated.

Before beginning a consideration of the treatment of pulmonic stenosis, I should like to mention briefly several other conditions in which the shunt, or by-pass operation, may be indicated.

MISCELLANEOUS CONDITIONS

The first to be considered is coarctation of the aorta. Doctor Park and I¹⁴ showed experimentally that the transposed subclavian artery is capable of conducting sufficient blood to maintain life in animals in which the thoracic aorta is completely occluded. This method has been used in the treatment of only one patient* with coarctation because the method described by Crafoord,¹⁵ and by Gross,¹⁶ in which the stenotic area is excised and an end-to-end anastomosis performed, appears to be a better one. I believe, however, that there will be occasions when the use of the subclavian artery to by-pass the point of stenosis, or atresia, of the aorta will be indicated. For example, it may not be possible to perform excision and an anastomosis in the infantile type of coarctation in which the constricted zone is longer than in the adult type. In addition, the use of the subclavian artery as a by-pass may be advisable in the treatment of coarctation in adults in whom the aorta is diseased and inelastic.

The splenic artery may be used for conducting blood to the left kidney. Dr. Richard Kieffer and I¹⁷ showed experimentally that when the divided proximal end of the splenic artery has been connected to the distal end of the divided left renal artery there has been no evidence of renal failure even though the right kidney is removed. It is unlikely that this particular method will have clinical significance since disease limited to the first part of the renal artery is very rare. Another possible use of the splenic artery is as a replacement for the first part of the superior mesenteric artery.

Dr. William Longmire¹⁸ has recently anastomosed the internal mammary vessels to the mesenteric vessels of a segment of jejunum which he was employing in the creation of an artificial esophagus. Easily palpable pulsations could be felt beyond the point of the anastomosis. Even though the lumen of the mammary vessels should subsequently become occluded, the procedure should prove helpful in maintaining viability of the intestine in the early critical

* This patient, unfortunately, has a partial paralysis of the lower extremities. In a recent personal communication, Dr. O. T. Clagett, of the Mayo Clinic, describes a brilliant result following the anastomosis of the subclavian artery to the aorta distal to the point of stenosis.

period before additional collateral pathways have had time to become enlarged.

In the treatment of an aneurysm of the first part of the common carotid artery in which the compression test indicates that ligation of the artery will not be tolerated, one might substitute the adjacent subclavian artery for the carotid. Ligation of the first portion of the subclavian is associated with little risk. There is not a great deal of difference in the caliber of the common carotid and subclavian arteries and an anastomosis is feasible.

Additional knowledge concerning the functions of the liver may make it advisable under certain circumstances to reroute the venous return from one or more of the abdominal organs in such a manner that the blood will return to the heart without passing through the liver. For example, it is possible, but not likely, that benefit would result from having the pancreatic venous return reach the heart without traversing the liver. Even if such were the case, however, the technical difficulties would be considerable.

It is unlikely that the reverse of the procedure which is used in the treatment of pulmonic stenosis can be used in the treatment of aortic stenosis. The success of the operation for pulmonic stenosis is dependent upon the higher pressure on the aortic side which causes blood to flow to the lungs. Even in the presence of severe aortic stenosis, the blood would probably flow from the systemic to the pulmonary system and the patient would not be helped.

The excellent course of most of the patients with the "tetralogy of Fallot" in whom an artificial ductus arteriosus has been established has made me wonder whether the associated interventricular defect does not serve as a safety valve in preventing heart failure. If this be true, the question arises whether induced interventricular and interauricular defects may not be helpful in the treatment of other cardiovascular abnormalities. Levine has aptly remarked that an automobile runs better with two flat tires than with one, and it may very well be that a balancing of the two sides of the heart may be desirable in the presence of certain unilateral abnormalities. In other words, the creation of an interauricular or an interventricular defect which will allow the blood to flow from a chamber with high pressure to one with a lower pressure may under certain circumstances be of an advantage.

A number of the ideas put forth in this section dealing with miscellaneous conditions are based upon theory and have not been put to practical test. Such is fortunately not true to the same extent in pulmonic stenosis, the subject to which we will now turn.

PULMONIC STENOSIS OR ATRESIA

The most frequently encountered type of congenital cardiovascular defect accompanied by cyanosis is the "tetralogy of Fallot," which is characterized by pulmonic stenosis or atresia, interventricular septal defect, dextroposition of the aorta, and right ventricular hypertrophy. Prior to the initiation of the work by Doctor Taussig and myself,¹⁹ only one attempt had been made by operative means to increase the circulation to the lungs in the treatment of pulmonic stenosis. The operation performed by Doyen,²⁰ in 1913, consisted

of an attempt to divide what was believed to be a stenotic valve with a tenotome knife. The patient died several hours later, and examination revealed the usual finding of narrowing of the conus rather than stenosis of the valve. It is only necessary to examine an autopsy specimen of a stenosis of the conus to realize that division of this area would not only be dangerous but would very likely not result in permanent improvement. The stenosis would probably recur even if the area were excised.

It is rather strange that previous attempts to improve the condition of patients with the "tetralogy of Fallot" by the construction of an artificial ductus had not been made. The fact that the volume of the pulmonary blood flow is greatly decreased must have been recognized. The realization that there were associated abnormalities such as the interventricular defect and the overriding aorta probably caused doubt as to the value to be derived from an operation. Furthermore, it was probably not realized that one of the branches of the arch of the aorta can usually be connected to a pulmonary artery without great difficulty. In the beginning we were somewhat skeptical as to the benefit that might be derived from the making of an artificial ductus, but the results of experiments encouraged us to proceed. Even then, I was fearful that cyanotic children would not withstand anesthetization and temporary occlusion of one of the two pulmonary arteries. Furthermore, it was feared that the use of the subclavian artery would result in ischemia of the arm. Experience²¹ has shown that our apprehension was in the main unwarranted—most of the children survive the operative procedure, and the collateral circulation to the arm is adequate.

The underlying principle in the choice of patients for operation is that there be inadequate flow of blood to the lungs. The history and the results of physical examination are of some aid. The two outstanding diagnostic features are roentgenographic evidence that the pulmonary artery is small in size and clinical and roentgenographic evidence of absence of congestion in the lung fields. Doctor Taussig and her associates have shown remarkable skill in diagnosing the condition correctly. Additional help has been supplied in recent months by Dr. Richard Bing, who has developed methods by which the blood flow through the pulmonary arteries, the total pulmonary blood flow including that through collateral channels, and the systemic blood flow can be determined with a fair degree of accuracy. These new tests have been of great aid in arriving at a correct decision in doubtful cases. Another diagnostic method which should be available and which we have not used to the desired extent is that of visualization of the heart and great vessels after the injection of radiopaque substances. The technics are available and the method should be employed.

It is now possible to predict with a fair degree of accuracy the danger associated with the operation in individual patients. In patients between the ages of two and twelve years in whom there is a typical "tetralogy" with a small heart, the mortality rate should be less than 12 per cent. When, however, atypical conditions such as a large heart, a large aorta, rotation of the heart,

situs inversus, or left axis deviation are present, the danger associated with the operation increases considerably.

The ages of patients who have been operated upon have ranged from four months to 26 years. The age preferred is from three to ten years. The operation is accompanied by a higher mortality rate in infants under two years of age. Operation is not advised in those 18 months and younger, unless the child is doing very poorly and it appears that the chances of survival to an older age are less than 50 per cent. The operation is usually more difficult from a technical standpoint in patients who have attained most of their growth. This is due to the fact that the gap to be bridged by the subclavian artery is greater in proportion to the length of the artery. Furthermore, the structures do not seem to be as elastic and pliable as in younger subjects.

There has been no recent change in our ideas as to the type of anastomosis or the choice of systemic vessel. An end-to-side anastomosis—that is, the union of the end of the systemic artery to the side of one of the two pulmonary arteries—is much to be preferred to an end-to-end union. The end-to-side anastomosis not only allows the blood to flow to both lungs but it exposes the patient to less risk of the development of pulmonary edema and heart failure. Furthermore, the end-to-side anastomosis does not preclude the possibility of a similar operation being performed on the opposite side at a later date.

In most patients who are more than two years of age the subclavian artery is the vessel of choice. The use of this vessel decreases greatly the danger of cerebral difficulty which may be associated with ligation of the innominate or carotid artery. In addition, there is less danger of heart failure as a result of the establishment of the fistula. Using the figures for arterial oxygen saturation reported by Doctor Taussig and myself, Dr. C. S. Burwell²² has shown that additional elevations of arterial oxygen saturation after a rise from a low level to 75 to 80 per cent is attained may be reached at considerable expense in terms of cardiac strain. The arterial saturation in patients with the “tetralogy of Fallot” will never reach the normal level of 96 per cent, regardless of the caliber of the artery used, because of the admixture of venous and arterial blood as a result of the septal defect. The desired aim is to use a systemic artery which is of such a caliber that the polycythemia and cyanosis will disappear but which is not large enough to place undue strain on the heart. The subclavian artery seems to be large enough in most patients more than two years of age. This statement should be qualified by saying that the size of the fistula may prove to be inadequate in some of these children as they increase in size. If so, the operation can be repeated on the opposite side. It has not yet been determined whether the fistula will increase in size with the growth of the patient. At any rate, it appears at the present time that the subclavian artery should be used when its caliber indicates that it will conduct sufficient blood to the lungs to cause a disappearance of the polycythemia and cyanosis; otherwise the innominate or carotid artery should be chosen.

In patients under 15 years of age the incision in the chest is usually made on the side opposite to that on which the aorta descends. In approximately one

patient in five the aorta descends on the right rather than the left. The innominate artery arises on the side opposite to that on which the aorta descends. It is desirable to use the subclavian branch of the innominate rather than the opposite subclavian which arises directly from the aorta since the former vessel makes a less acute angle with its parent artery after the anastomosis is performed.²³ Furthermore, exposure of the innominate allows one to use this artery or its carotid branch if the subclavian artery is too small or too short. In older patients with long chests, there may be difficulty in approximating the subclavian artery to the pulmonary. For this reason, at times we utilize the subclavian branch of the aorta in the older age-group even though the resulting angulation is not desirable.

Probably the most frequent error that will be made in the performance of this operation will consist in mistaking the pulmonary artery to the right upper lobe for the main right pulmonary artery. In approximately one patient in five, the main right pulmonary artery divides early. The branch to the middle and lower lobes may arise in the mediastinum at the pericardial reflection. Unless one realizes this fact, one may perform, or attempt to perform, an anastomosis between the systemic artery and the pulmonary artery to the upper lobe. This is usually unsatisfactory because of the small caliber of the latter vessel. Unless the major branches to the right lung can be identified, one should persist in the dissection until the pericardial attachments have been freed and almost the entire length of the right pulmonary artery has been exposed. In this discussion the right side has been emphasized because early branching of the left pulmonary artery appears to occur less frequently. It should be added that the dissection is difficult if there are dilated collateral arterial pathways.

Difficulty may arise in identifying the pulmonary artery of one of the lungs and in distinguishing it from a pulmonary vein. This is particularly apt to occur if the pulmonary artery is diminutive in size and in an abnormal location. Furthermore, it is well to remember that the pulmonary artery may be absent. The position and course of the vessel and the pressure within the vessel are of aid in identification.

A sterile apparatus with which the pressure in the pulmonary artery may be measured is available at all our operations. This consists of a syringe and needle which are connected to a water manometer. If the pulsations in the pulmonary artery are not easily visible, the pressure is not measured. If the pulsations are strong, thereby casting doubt on the correctness of the diagnosis of pulmonic stenosis, the pressure is measured. In the great majority of our patients the pressure has been under 240 mm. of water and the anastomosis has been performed. If the pressure is well in excess of this figure, there is a strong likelihood that the diagnosis is in error. It is important to emphasize that the caliber of the pulmonary artery is not a good index of the pressure within the vessel. The pressure in several of the largest pulmonary arteries has been quite low.

As I stated previously, an end-to-side anastomosis is much to be preferred

to an end-to-end one. When the systemic artery is short, there may be considerable difficulty in performing the operation. If the anastomosis can be carried out by the use of fine suture material, the tension in the postoperative period will not be too great to prevent healing. After the instruments are removed and the lung is reinflated, the tension on the suture line appears to diminish. There has been no instance in which the vessels have separated. The most important points in technic are placing the sutures in such fashion that the intima is everted and adventitia is not pulled between the intimal surfaces, and taking care that the sutures are not pulled too tightly.

The average time required for the operation has been approximately two hours. In the majority of cases, no great haste is necessary. In the occasional patient, however, occlusion of one of the pulmonary arteries is tolerated poorly and the more quickly the anastomosis is performed the better.

My associates and I have now operated upon 243 patients who were thought to have the "tetralogy of Fallot." The over-all mortality rate, including deaths among those in whom an anastomosis could not be performed, those in whom the diagnosis was in error, and those who have died since leaving the hospital, has been 21 per cent. The mortality rate in the second 100 patients was 15 per cent. In the patients (approximately 147) in whom an anastomosis between the end of a subclavian artery and the side of the pulmonary artery was performed the mortality rate was 9 per cent. On the other hand, the mortality rate among those in whom the carotid or innominate artery was used (approximately 57) was 33 per cent. It is only fair to state that the long waiting list of patients has more or less forced us to choose for early operation those patients who are doing rather poorly and for whom postponement of operation would be a serious risk. Even so, 20 or more patients have died while awaiting admission to the hospital.

The follow-up periods are still of too short duration to allow evaluation of the final results. It can be stated that many of the children appear to be normal, that cardiac enlargement after the first several weeks is not progressive, and that, thus far, *Streptococcus viridans* infection has not developed. There have been no instances of empyema or mediastinitis.

SUMMARY

The purpose of this lecture has been to discuss certain abnormalities of the circulatory system in which treatment by shunt or by-pass operations is proving effective or may be found to be useful. Particular emphasis has been placed on the treatment of portal hypertension and pulmonic stenosis. It is hoped that the advances thus far recorded will serve as an added stimulus for further studies in which efforts will be made to improve the arterial in-flow or the venous return of important organs.

REFERENCES

- 1 Owings, J. C.: Successful Experimental Ligation and Division of the Thoracic Aorta. *ANNALS OF SURGERY*, 115, 596, 1942.
- 2 Beck, C. S.: Development of a New Blood Supply to the Heart by Operation. *ANNALS OF SURGERY*, 102, 801, 1935.

- ³ Blakemore, A. H., and Lord, J. W., Jr.: A Nonsuture Method of Blood Vessel Anastomosis. *J. A. M. A.*, 127, 685, 1945.
- ⁴ Johns, T. N. P.: Unpublished observations, 1946.
- ⁵ Crafoord, C., and Gross, Robert: Discussion at Meeting of Amer. Assoc. of Thoracic Surgeons, Detroit, Mich., May, 1946.
- ⁶ Whipple, A. O.: The Problem of Portal Hypertension in Relation to the Hepatosplenopathies. *ANNALS OF SURGERY*, 122, 449, 1945.
- ⁷ Rousselot, L. M.: The Late Phase of Congestive Splenomegaly with Hematemesis but without Cirrhosis of the Liver. *Surgery*, 8, 34, 1940.
- ⁸ Blakemore, A. H., and Lord, J. W., Jr.: The Technic of using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension. *ANNALS OF SURGERY*, 122, 476, 1945.
- ⁹ Eck, N. V.: The Ligature of the Portal Vein. *Voyeno Med. Jour.*, 1877.
- ¹⁰ Quievolo, G. B.: Eine Neue Methode Zur Vereinigung der Venen. *Untersuch. Zur Naturlehre des Menschen und der Thiere*. Moleschott, 15, 233, 1893-95.
- ¹¹ Rosenstein, P.: Über Die Behandlung der Leber Cirrhose durch Aulegung einer Eckschen Fistel. *Arch. f. Klin. Chirurgie*, 98, 1082, 1912.
- ✓¹² Whipple, A. O.: The Rationale of Portacaval Anastomosis. *Bull. New York Acad. of Med.*, 22, 251, May, 1946.
- ¹³ Blakemore, A. H., Portacaval Anastomosis: A Report of Fourteen Cases. *Bull. New York Acad. of Med.*, 22, 254, May, 1946.
- ¹⁴ Blalock, A., and Park, E. A.: The Surgical Treatment of Experimental Coarctation (Atresia) of the Aorta. *ANNALS OF SURGERY*, 119, 445, 1944.
- ¹⁵ Crafoord, C., and Hylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment. *Jour. Thoracic Surg.*, 14, 347, 1945.
- ¹⁶ Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta; Experimental Studies Regarding its Surgical Correction. *New England Jour. Med.*, 233, 287, 1945.
- ¹⁷ Kieffer, R., and Blalock, A.: Unpublished observations, 1946.
- ¹⁸ Longmire, William: Unpublished observations, 1946.
- ¹⁹ Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart in which there is Pulmonary Stenosis or Pulmonary Atresia. *J. A. M. A.*, 128, 189, 1945.
- ²⁰ Doyen, E.: Chirurgie des Malformations Congenitales on Acquises du Coeur. *Cong. Franc. de Chir., Proc. Verb.*, 26, 1062, 1913.
- ²¹ Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects. *Bull. New York Acad. of Med.*, 22, 57, 1946 (Harvey Lecture).
- ²² Burwell, C. S.: Personal communication, 1946.
- ²³ Blalock, A.: The Surgical Treatment of Congenital Pulmonic Stenosis. *ANNALS OF SURGERY*, 124, 879-887, November, 1946.

THORACIC SURGERY IN A HOSPITAL CENTER

COL. LAURENCE MISCALL, M.C.,

AND

MAJOR ALBERT W. HARRISON, M.C.

PART I

THE DATA from the records of 300 patients treated for thoracic battle injuries since D-day in the 804th Hospital Center, supplies the material for this report. It will be presented under three broad aspects:

- (A) A review of the situation before admission to the Thoracic Center.
- (B) A report of activities in the Thoracic Center.
- (C) Recommendations for the care of thoracic casualties.

A—SITUATION BEFORE ADMISSION TO THE THORACIC CENTER

Records.—Many records have lacked final diagnosis, operative findings and procedure, details of specific treatment and laboratory and roentgenologic reports. This has precluded uniform comparative statistical study and provided frequently an uncertain basis for continuation of therapy.

First-aid and Emergency Care.—Treatment at all forward echelons has been reduced to essentials. The necessity for prompt control of hemorrhage, immediate restitution of cardiorespiratory function and prevention of infection have been fully appreciated. Packing and occlusive dressing of sucking wounds, positioning, sedation and early chemotherapy have been effectively used on the field. Treatment has progressed through ensuing stations. Plasma has been used freely in shock. A few sutures or ligatures have improved hemostasis and wound closure. Hemothorax and tension pneumothorax have been recognized and relieved by aspiration as indicated. After these simple measures, excellent judgment has governed priority of evacuation. Medical personnel should realize that these conservative measures have preserved many patients for subsequent care and cure in hospitals.

Field and Evacuation Hospitals.—At the Field and Evacuation hospitals, diagnostic aids and surgery have been judiciously employed in spite of many difficulties.

Shock.—Shock therapy has been necessarily continued in the majority of cases. As much as 3,500 cc. of blood and plasma have been given in 24 hours, usually with life-saving results. When the accentuation of shock by hemothorax, tension, cardiac injury and anoxia has been occasionally overlooked, large infusions of any type have precipitated serious episodes. Occlusion of wounds, pleural and bronchial aspiration, oxygen and replacement of blood loss have generally sufficed either to cure or carry the patient to operation in optimum condition. In some extensive injuries emergency surgery has been imperative to control shock and has given many results which must be considered excellent in such grave situations.

Wounds.—After recovery from shock, or when otherwise indicated, wounds have been well-attended. The relative constancy in each type deserves some mention for the aid it may lend in the future.

Tangential nonpenetrating wounds associated with thoracic damage necessitating evacuation to the Center have not been common. Severe atelectasis has been seen more often than extensive hemorrhagic consolidation. It has yielded to clearing of the air-ways. Hemorrhagic pneumonitis, except the massive type, had generally cleared without treatment before admission to the Center. Both have been confused with fluid and nonproductive aspiration repeated in spite of rather typical signs, symptoms and roentgenograms. Hemothorax has often followed but has required frequent tapping only when atelectasis or other factors caused persistence. These wounds have presented few thoracic problems.

Rifle bullets have often pierced the thorax without immediately serious consequences. Small nonsucking wounds, minimal hemothorax and lack of pulmonary collapse have been noted frequently. Direct tracts have been visualized on early roentgenograms as a hole through lung with circumferential clouding, presumably hemorrhagic pneumonitis, which has not exceeded a lobar distribution. Some with normal primary films have soon exhibited a massive atelectasis, of which concussion and retention of bronchial exudate have been prominent antecedents. Pneumonitis, atelectasis and other findings have cleared as early as seven days after injury, with complete healing in four weeks. Most have recovered without admission to the Center with initial dressing, bronchoscopy, chemotherapy, sedation, rest and occasional thoracentesis. Suppuration has not been common in the few requiring further treatment.

Shell fragments have produced fairly typical patterns. Small ones with little inertia have produced small nonsucking wounds, minor lung trauma and limited hemothorax or hemopneumothorax. With rapid sealing of visceral pleura retention of them has been frequently asymptomatic and not always injurious. Early recovery with conservatism has been quite uniform. Few have required secondary surgery except for extraction of the fragments. Large missiles have usually had a different course due to their size, ragged shape and motion. Open or sucking wounds, major loss of tissue, marked hemothorax, tension and imbedding of foreign material have been common. Such wounds usually have required débridement and intuitive plastic closure. Severe clinical condition has persisted until admission to a hospital, in spite of prompt first-aid. Resources have been taxed to supply the necessarily intensive therapy of shock, hemorrhage and tension so common in these patients.

Hemothorax and Hemopneumothorax. — Hemothorax or hemopneumothorax have been rather constant. They have responded usually to aspiration and penicillin. Primary closed drainage has been necessary often because marked hemopneumothorax and tension have repeatedly recurred after extensive trauma. In these difficult cases it has been superior to repeated aspiration or the flutter-valve. Some poor results have occurred because such primary drainage has not been used to meet these adverse conditions.

Exploratory Thoracotomy.—When conservative measures have not

promptly restored and adequately maintained cardiorespiratory function, surgical approach to the problem has been imperative. Results have been impressive. Intrathoracic procedure has been principally concerned with control of hemorrhage, repair of lacerations of the lung, diaphragm and viscera and removal of some large foreign bodies. Patients *in extremis* have bounded back because of surgical reestablishment of circulation and respiration. Half-measures have given way to definitive surgery when the problem has been clearly appraised and skilfully managed.

The excellence of some results warrants brief comment on the mistakes. Pentothal or local anesthesia have been utilized to avoid the more time-consuming administration of a general anesthetic with endotracheal technic. The inability to control respiration has prevented or prematurely terminated some advisable operations. Continuing hemorrhage has not been promptly recognized and controlled. Inattention to the flooding of the air-ways has predisposed to atelectasis. Unnecessary sacrifice of ribs and soft tissues has promoted chest wall flaccidity, embarrassed respiration and complicated subsequent course and treatment. Late complications have been closely related to the retention of foreign bodies, inadequate closure of lacerations of the lung or diaphragm and insufficient drainage.

Chemotherapy.—Local and systemic sulfa-therapy has been started, almost without exception, on the field soon after injury. Irregularly in the hospitals it has been continued and supplemented or displaced by the administration of penicillin. More carefully controlled records are essential before the exact benefit of each agent can be more than an impression.

Evacuation.—With few exceptions, patients have arrived at the U.K. Base Hospitals in excellent condition. The early medical care, holding of patients and air evacuation, which has not been hazardous, have been largely responsible for this. With slow evacuation by train and repeated hospitalization, continuity of medical supervision has been lost. Lack of treatment in transit has predisposed to an increase in the number and the complexity of secondary operations, with a corresponding reduction in the ability to return to duty. When evacuation has been slow, intensive conservative therapy has been extremely valuable in situations not always subject to prompt improvement. Rapid evacuation has distinct military value in the increased numbers of wounded who return to duty because they either avoid surgery or receive it before chronicity demands major procedures and long convalescence.

General Hospitals (U. K.).—Despite all forward efforts hemothorax and hemopneumothorax have been the commonest initial problems at the General Hospitals. By aspiration the pleural space has been maintained as dry as possible. As much as 1,200 cc. of blood and air have been removed at one time. Any one aspiration has been discontinued at the onset of disturbing dyspnea, cyanosis, cough, tightness, tachycardia, or shock. After each aspiration 40,000 units of penicillin in 10 cc. of saline have been instilled. Table I details the data available on 100 patients clearing with this therapy. Sixty-nine cases without primary drainage cleared completely on five taps during which an

THORACIC SURGERY CENTER

average maximum total of 2,900 cc. was removed. Thinning to serous quality, progressive clearing of roentgenograms and clinical improvement have been the best guides in treatment. Twenty-four other patients in whom more serious injury was treated by primary closed drainage recovered with subsequent treatment as shown on Table I. It is significant that 15 of these cases required

TABLE I
DETAILS OF ASPIRATION AND CHEMOTHERAPY IN 100 CASES NOT REQUIRING
SECONDARY OPERATION AT THE THORACIC CENTER
NO PRIMARY DRAINAGE

No. Aspira- tions at Center	No. of Cases	Avg. Total Removed. Cc.	Adequate Chemo- therapy	Inadequate Chemo- therapy
1	5	0
1	13	375	8	4
2	18	1,000	7	2
3	18	1,100	9	1
4	6	1,600	2	2
5	9	2,900	5	1
	—		—	—
	69		31	10

PRIMARY DRAINAGE

No. Aspira- tions Postoper.	No. of Cases	Avg. Total Removed Cc.	Adequate Chemo- therapy	Inadequate Chemo- therapy
0	15	0	5	4
1	0	0	0	0
2	6	700	3	1
3	0	0	0	0
4	0	0	0	0
5	3	2,200	2	0
	—		—	—
	24		10	5

no subsequent aspiration and six were cured with two aspirations. In three cases needing five or more aspirations, the drainage tube had been removed in less than 48 hours, which appeared insufficient for stabilization of the pleura.

Chemotherapy, particularly intrapleural penicillin, probably has contributed to recovery without suppuration in this group since the fluid was definitely contaminated in ten cases. Yet this success cannot be resolved solely in its favor. The resistance of the pleura to infection, correction of anatomic defects, removal of the culture medium and obliteration of the pleural space by prompt lung expansion may have been underestimated. The complete recovery of 15 patients (Table I), whose records indicate totally inadequate chemotherapy, supports the contention that these factors are of great importance.

In a survey of 500 admissions to all hospitals, 70 per cent of hemothoraces have been observed to clear all chest symptoms, signs and roentgenograms in four to six weeks with such conservative therapy. Close scrutiny did not reveal any thoracic contraindication to early return to full duty. Medical officers have not been always quick in recognizing the necessity of surgery with the failure of these measures. Continuation of ineffective methods has allowed frequent progression to chronicity before transfer to a Thoracic Center.

B—ACTIVITIES AT THE THORACIC CENTER

The concentration of the resistant cases in Centers has yielded many observations upon which the efficiency of present methods may be partially evaluated. Although the transient follow-up, lack of comparative control series and other factors, prohibit sound deductions in many specific problems, significant facts deserve consideration as tentative guides for the future.

All patients have been admitted to the Thoracic Center for treatment of sequelae which can be broadly classified as follows:

1. Persistent hemothorax or hemopneumothorax. The fact that they have been clotted and unclotted; contaminated and uncontaminated; suppurative and nonsuppurative with and without underlying pathologic findings has added to the complexity of the problem.
2. Abdominothoracic injuries.
3. Retained foreign bodies.

Persistent Hemothorax and Hemopneumothorax. — In considering this problem it is important to ascertain why and when they are persisting before any logical step in diagnosis and treatment can be taken. In this survey these factors have been found to predispose to such persistence or recurrence.

1. Inadequate aspiration has often resulted from difficulties introduced by the military situation, associated injuries, evacuation and other events. Circumvention of these has received resourceful attention which has not always succeeded. The failure to aspirate small amounts has been an error. They have concealed foreign bodies, clotted, and become infected often. Nonremoval of air in the presence of blood has promoted multiple loculation, with subsequent inability to clear the pleural space by aspiration and expand the lung. This has been followed frequently by infection.

2. Atelectasis has been frequently overlooked. The early appearance of dyspnea, cough, physical signs and ground-glass roentgenograms with elevated diaphragm and retraction to the affected side with a previous history of pulmonary concussion, bloody or mucoid sputum, tangential or open-wounding, operation and shock have been typical. Symptoms and rapid reaccumulation after moderate aspiration (500 cc.) have repeatedly indicated its presence. Instillation of air to relieve symptoms has caused multiple loculation. Pleural fluid and atelectasis have subsided following bronchoscopic relief as late as 21 days after trauma.

3. With metallic foreign bodies in or communicating with the pleural space, fluid has persisted, recurred or become infected. Even small bodies near subpleural vessels have caused late serious hemorrhage. Chemotherapy has enhanced results when removal has been unavoidably delayed.

4. Residual defects have been prominent offenders. Bronchopleural fistulae have been almost universally associated with recurrent hemopneumothorax. Although brisk hemorrhage from lung has been rare, parenchymal tracts have continued to weep. Subpleural abscesses have often stimulated effusion and by rupture have produced empyema. Such defects have not been corrected by exploration, as indicated by the routinely poor reaction to primary treatment.

5. The neglect and misuse of closed drainage have led to much reaccumulation, which has often exceeded the range of applicability of aspiration. When it has been discontinued before stabilization and subsidence of pleural secretion, multiple loculation and infection have been usual.

6. Abdominothoracic wounds which deserve separate comment complete the list of common causes.

Information denoting abnormal persistence and the activity of these factors has been available but not carefully regarded. The figures from 72 operative cases are illustrative. In 47 of them aspiration in excess of five taps of 2,900 cc. was not accompanied by the usual signs of improvement. In the other 25, clotting prevented withdrawal of fluid. Ineffective aspiration was continued and progress for which surgery offered the only solution was not recognized in many until suppuration had resulted.

The futility of continuing conservatism under such circumstances may be clarified after a review of the pertinent facts. Blood in a chest compresses lung and will clot in time. A tough, inelastic, fibrohemorrhagic membrane organizing on the parietal and visceral pleura immobilizes lung, chest wall and diaphragm. It soon becomes difficult to separate. Since the chief surgical implication has been the membrane rather than the clot, "constrictive pleuritis" has seemed a better term than "clotted hemothorax." Reduced breathing capacity of fused chests makes pulmonary cripples of such patients. In a surprisingly short time (two to four weeks) the membrane has become so inelastic that neither aspiration nor drainage permit the lung to expand properly. Nothing short of removal of the membrane, decortication, has sufficed. If this has been delayed too long, infection has often supervened. Suppuration in the clot encased by the membrane has given empyemata that are chronic at inception. Bronchopleural fistulae, foreign bodies and pulmonary suppuration have been prominently associated with such developments. Chemotherapy has played a

TABLE 11
THORACIC DISTRIBUTION OF 200 CONSECUTIVE OPERATED PATIENTS
804th Hospital Center—U. S. Army

Diagnosis	Number	% Total
1. Empyema, acute.....	14	7.0
2. Constrictive pleuritis (clotted chest, simple).....	29	14.5
3. Constrictive pleuritis (suppurative).....	39	19.5
4. Abdominothoracic injuries	28	14.0
5. Foreign bodies.....	98	49.0
(elective removal):		
a. Heart and great vessels.....	20	
b. Mediastinum.....	10	
c. Lung and pleura.....	68	
6. Foreign bodies.....	40	
(incidental removal):		
a. Pleura.....	15	
b. Lung.....	25	
<hr/>		
Total operated patients.....	200	
Total operated for suppuration.....	81	40.5
Total with complications of hemo- or hemopneumothorax,	82	41.0
Total with suppurative complications of hemo- or hemopneumothorax.....	53	65.0

REPRESENTATIVE ROENTGENOGRAMS

Figures 1-2 and 3 illustrate hemothorax without suppuration. Hemothorax with suppuration is shown in Figures 4-5 and 6.

FIG. 1-A

1-B

1-C

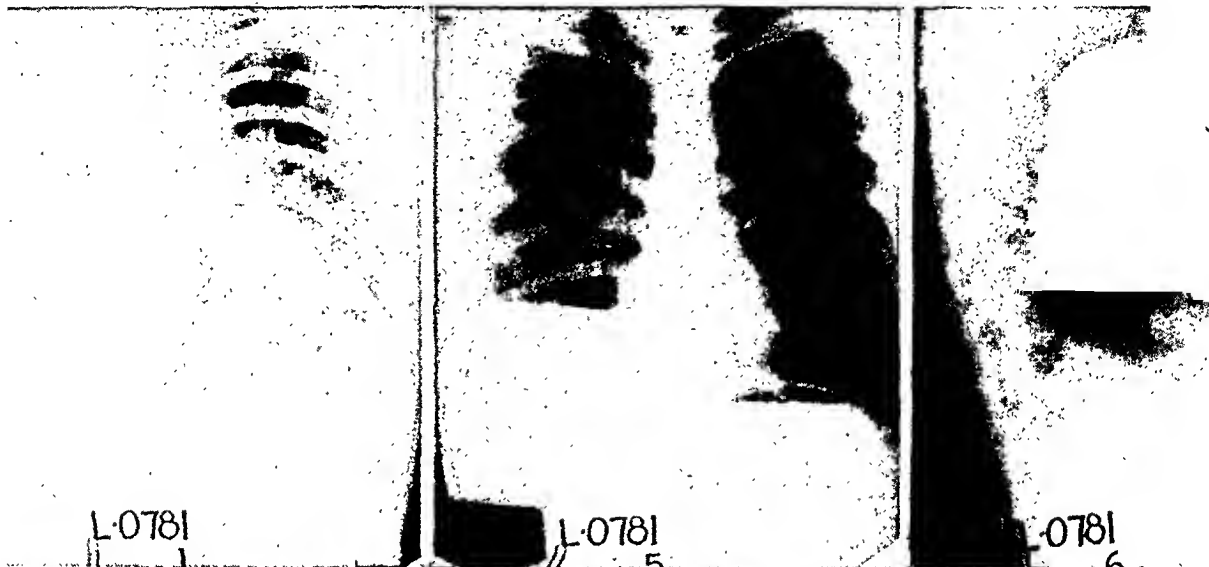


FIG. 2-A

2-B

2-C

FIG. 1.—L-0781: Injured: August 1, 1944. Penetrating wound of right chest.

A.—August 8, 1944. Constrictive pleuritis (clotted massive hemothorax).

B and C.—October 15, 1944. Result 33 days after decortication. Contaminated with *Staphylococcus aureus*.

FIG. 2.—F-0285: Injured: August 23, 1944. Multiple rib fracture with left hemothorax.

A.—August 30, 1944. Left hemothorax.

B.—September 19, 1944. Multiloculation after instillation of air.

C.—September 30, 1944. Result after intensive aspiration, penicillin and thoracic exercise for 10 days.

significant rôle in delaying suppuration. This has flared up when discontinuation of sulfa-drugs and penicillin, clotting or reinfection through fistulae have recreated the essentials for progress. Blanket use of these drugs has been no substitute for sound surgical procedure in this problem. Further subdivision of persistent hemothoraces is based upon characteristics which have seemed to justify some regimentation of treatment.

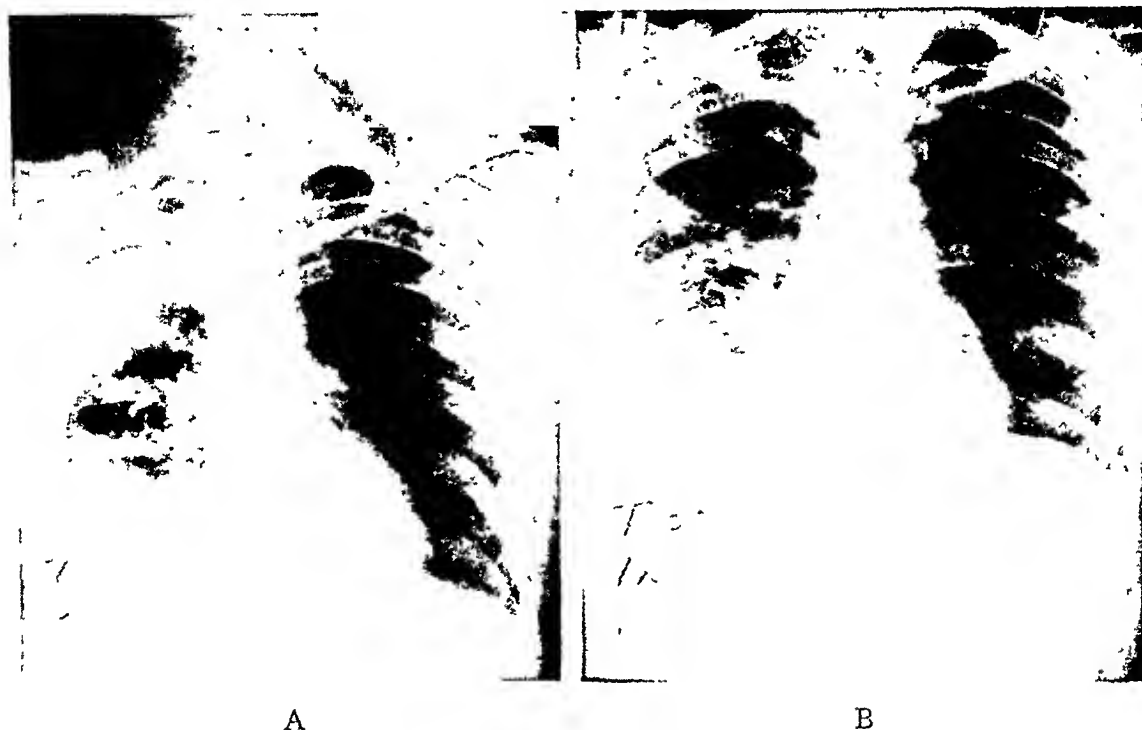


FIG. 3.—T-3501: Injured: February 7, 1945. Penetrating wound right chest. Retained shell fragment right lung.

A.—March 3, 1945. Constrictive pleuritis right.

B.—March 12, 1945. Result seven days after decortication.

(A.) Persistent hemothorax or hemopneumothorax in which organization has not precluded expansion by conservative measures.

(B.) Persistent hemothorax or hemopneumothorax in which organization has precluded expansion by conservative treatment. Invasion by pathogenic organisms has generally proceeded to suppuration unless prevented by early surgical intervention. Multiloculated hemothorax, acute empyema, simple constrictive pleuritis (clotted chest) and suppurative constrictive pleuritis represent various degrees in this process. The distribution is outlined in Table II.

(A.) *Persistent Hemothorax, etc., Amendable to Conservative Treatment.*—With apparent failure of conservative measures in other hospitals, many patients have been referred to the Thoracic Center for operation. Untreated atelectasis and incomplete aspiration have contributed to many of these failures. After careful reëxamination, aspiration drainage of all pleural collections was repeatedly practiced. The air-ways have been cleared by bronchoscopy, cough, postural drainage and other methods. Breathing exercises by the patient have been carefully supervised, rigidly enforced by schedule, and pushed to the

200-1040



14-P-1040

C

150



A

B

FIG. 5.—R-1091: Injured: February 2, 1944. Sucking wound left chest.

A.—March 12, 1944. Left suppurative constrictive pleuritis. Bronchopleural fistula. (Pyopneumothorax, suppurative hemopneumothorax—*Staph. and Strept.*)

B.—March 20, 1944. Result 24 hours after decortication, segmental resection of left upper lobe and closure of fistulae. Note two tubes for drainage.



A

B

FIG. 6.—L-7880: Injured: September 27, 1944. Penetrating wound left chest.

A.—October 11, 1944. Left constrictive pleuritis suppurative. (Pyopneumothorax in clotted hemopneumothorax, *Staph. aureus.*) Subpleural abscess of right lower lobe around retained foreign body (circled).

B.—October 29, 1944. Result 12 days after decortication, resection of abscess area and removal of foreign body from right lower lobe.

limit of tolerance. They have proven to be a valuable adjunct in the therapy and rehabilitation of all chest cases.

The presence of pathogenic organisms did not confuse the issue. The report of positive cultures in 10 per cent of the cases is likely low, due to previous use of penicillin. If pus has not been obtained, surgical intervention, perhaps necessary later, has not been indicated immediately. Aspiration drainage with instillation of 40,000 units of penicillin has been continued with excellent results as long as clinical and roentgenographic improvement were observed. No patient has been considered for operation unless a static or regressive course has been proven after thorough trial (10 to 14 days) on such a regimen. Persistence in the use of these methods has increased the number of patients who, recovering without operation, have returned to duty.

(B.) *Persistent Hemothorax Amenable Only to Surgical Treatment.*—The segregation of these cases has permitted early operation, which has reduced procedural difficulties incident to delay.

Multiloculated Hemopneumothorax.—Not only have few badly-loculated hemopneumothoraces responded to aspiration but many have clotted and suppurated. They represent the earliest stage of simple constrictive pleuritis with which they are grouped. They have been decorticated promptly, at which time ease of operation has been equalled by excellence of results.

Acute Empyema.—The poorly-treated hemothorax has provided a fertile field for the development of acute empyema. The 14 cases of acute empyema which have been admitted to the center comprise 17 per cent of the 82 cases submitted to surgery for complications of hemothorax. All have exhibited certain characteristics. Initial injury had been considered to warrant only simple wound closure in all except four cases. Minimal hemothorax had had uniformly poor aspiration and chemotherapy. Only two had been primarily drained. Five had retained metallic pleural foreign bodies. These conditions had contributed to the onset of empyema of acutely clinical type and of relatively small size. Pus had developed in all cases within 12 to 14 days after injury, and contained the organisms listed. Closed drainage soon after admission was converted in ten days to open-type, with rib resection in ten cases. Initial rib resection and open drainage were used in four cases. All intrapleural foreign bodies were removed at the first operation, regardless of the type of drainage instituted. The local and systemic use of penicillin has not appeared to add much to adequate dependent drainage, and has not been routine. All patients recovered but few were completely healed in less than 60 days after injury.

Early suppuration in extensive hemothoraces has been surgically drained in many hospitals along the line of evacuation. They have reached the Center in good condition for residual care. However, five chronic empyemata required decortication at the Center because of premature, ill-advised or poorly-executed open drainage.

Constrictive Pleuritis (Clotted Chest).—This diagnosis was substantiated by surgery in 29 cases and necessitated 35 per cent of the operations for com-

plications of hemothorax. Bullets (3) and shell fragments (26) had caused sucking wounds in 13 (44 per cent) of them. Only two had been primarily explored and three primarily drained. Metallic foreign bodies were free in the pleural space in two and sealed off in the lung in sixteen. Dyspnea has been the outstanding symptom; signs and roentgenograms have varied. Complete blotting out of the lung, multiple fluid levels, definite demarcation of the clotted area, and retraction to the affected have been typical. The contracted and immobile fused chest has usually not fully developed before 21 days after injury.

All were decorticated in an average of 35 days after trauma. Metallic foreign bodies and large rib fragments were uniformly removed from the lungs and pleural space. Small multiple rib fragments sealed-off in the lung were not disturbed. Two small pieces of metal were recovered by bronchoscopy and cough. Positive cultures were found in eight, or 27 per cent, of the cases. Five of these occurred with retained foreign bodies. All wounds healed by primary union. Twenty-seven patients were well, with closed, healed and non-draining chests after seven days. Two patients developed small collections of pus which cleared with early drainage. All were discharged for major rehabilitation in an average of 44 days after operation unless contraindicated by additional thoracic complaints.

Constrictive Pleuritis (Suppurative).—Suppuration complicated 39 cases of constrictive pleuritis. These represent 48 per cent of the operations for sequelae of hemothorax. These patients have generally been the more seriously injured. Sucking or open wounds caused by larger missiles occurred without exception. Hemopneumothorax rather than hemothorax had resulted in 34 (87 per cent) of the cases. Tension recurred in 11 (31 per cent). Many were multiloculated. Twenty, or 51 per cent, had persistent bronchopleural fistulae through which constant reinfection was probable.

Methods to combat the difficulties have not been uniformly successful. Intermittent aspiration and the flutter-valve have been most ineffective. Only 12 had been primarily explored and 11 drained. Original basal catheters have been too small, poorly placed and removed too early. Foreign bodies had been allowed to remain in eight (20 per cent) pleural spaces. Such bodies in eight (20 per cent) lungs were associated uniformly with bronchopleural fistulae. Abscesses occurred along six of the tracts and around one fragment. Surgery for simple constrictive pleuritis had been delayed in many until frank suppuration had appeared and increased the difficulty of operation.

All these patients were decorticated in an average of 58 days after injury. Preliminary closed drainage of eight cases (20 per cent) with a large tube has controlled excessive sepsis satisfactorily. Decortication has followed in about 14 days. All large metallic and other foreign bodies have been removed from the pleural space and lung. Ten segmental resections were completed for four abscesses and six fistulae. Three superficial small abscesses and 14 fistulae were excised and closed with reconstruction of pleural continuity.

Of 39 cases, 31, or 79 per cent, were completely healed with closed non-draining chests and expanded lungs in seven days. Eight patients (20

division at both ends, has insured adequate exposure. After evacuation of the pleural space, the limits at which the membrane is reflected from lung to the chest wall have been defined. To avoid laceration, the lung has been progressively mobilized toward the mediastinum as the rib-spreader is gradually opened widely. Removal of the tough constricting membrane from the entire lung, most of the chest wall and diaphragm has been a tedious procedure, frequently consuming four hours. Delay has invited infection and both have increased the difficulty of removal. The observation that mobilization of the entire lung has allowed it to expand more rapidly and normally has been substantiated by postoperative roentgenograms, and results. Such mobilization, regardless of extent of pleuritis, is now routine and deemed of vital importance in the speed and completeness of recovery which these patients have had. At least two multiple-holed catheter drains have been inserted routinely apart from the incision and have been sutured in place intrapleurally. One ascending anteriorly to the apex has insured evacuation of air without trapping around the upper lobe which, with rare exception, has expanded well. Another in a horizontal position in the upper limits of the costophrenic sinus has prevented early dependent accumulation of fluid. A third, suitably placed, has drained the gutter or site of marked suppuration or lung resection when necessary. After the instillation of penicillin (100,000 units in 15 cc. of saline) particularly around suppurating and resected areas, the chest has been carefully closed in layers. Divided rib ends and the ribs adjacent to the incision have been closely approximated by wire through drill holes. This, with anatomic repair of all soft tissue has given excellent wounds. After application of dressings, but just before removal from the table, suction of the catheters and bronchoscopy have permitted immediate lung expansion and practically eradicated tension pneumothorax and atelectasis.

Decortication has been carried out as soon as the diagnosis and a static or regressive state have been proven. The extensive empyemata which have occurred as the result of infection of previously persistent and clotted hemothoraces have always been chronic at inception. Simple drainage has been used in them only as a preliminary measure to improve poor clinical condition. Decortication has offered the only possibility of cure without protracted convalescence and multiple operations.

Several factors have favored the success of this procedure.

Meticulous attention to surgical technic with adequate exposure, visual dissection, gentleness with all tissues and thorough hemostasis have warranted the time spent. Fine interrupted cotton suture material has been used exclusively, without the appearance of any objection.

Decortication has been supplemented by any other procedure considered necessary to maximally approximate normal thoracic relations. Foreign body removal, closure of fistulae, resection of lung, repair of hernia, obliteration of dead space and reestablishment of pleural continuity have been uniform practices. Small superficial abscesses and fistulae have been excised and sutured

without parenchymal drainage. Large ones have been segmentally resected and closed with additional pleural drainage at the site.

Maximum preservation and reconstitution of the chest wall by intercostal incision and subsequent wiring through drill holes have preserved maximal functional apparatus and unity action of the wall in these frequently "shot-up" chests. Troublesome pericostal sutures have been avoided. These have perhaps enhanced the benefits of thoracic exercise which can and should be instituted postoperatively within 24 hours.

The ability to obtain and maintain prompt expansion of the lung, obliterate the pleural space and prevent accumulation of blood or other culture media have contributed most to the success of this procedure. Operation has not been considered complete until this could be done and all defects leading to the original condition corrected. In maintaining such conditions, multiple closed catheter drains have worked quite satisfactorily, and high negative pressure from suction pumps has not seemed necessary. They have been retained until clearing of the chest has signified obliteration of the pleural space from expansion. This has usually taken four to five days, during which time gentle irrigation with penicillin (250 units per cc.) has maintained patency of the tube. On few occasions they have been left in place as drains of small collections and gradually withdrawn with tract irrigation. Intrathoracic penicillin has inhibited infection in the ever-present minimal fluid which collects in spite of drainage. Intramuscularly (120,000 units daily for five days), it has protected the wound until body forces can take over complete control.

Results have been considered good enough to warrant further trial of these procedures. Empyemata amenable to classical drainage methods have been in the minority in this Center. The ability to obtain a closed nonsuppurating pleural space in less than 14 days in 80 per cent of patients operated upon for suppurative constrictive pleuritis has influenced the writers to use decortication increasingly. The recurrence of empyema in 20 per cent of them has not been considered a valid objection, since they have been small and have responded well to prompt drainage, with a marked reduction in the duration and severity of illness. No chest wall phlegmons nor other feared sequelae have arisen. These results have seemed to further justify the prompt use of decortication immediately after clotting to avoid the risk of suppuration. By some this has been called radical surgery. Yet in this series, 75 decortications, many in the face of severe infection, have carried no mortality, and the number continues to grow in this as well as all other Thoracic Centers. Although the closed chest may be a boon to medical personnel, it has been little short of a blessing to patients and most gratefully received by them. Neither early neglect of conservative measures nor retreat before the misnomer, "radical surgery," should deny promise of cure to any patient. One can look forward to less decortication and better results from more preventive surgery at the forward stations rather than by adoption of less satisfactory measures in the Centers.

(TO BE CONTINUED)

WAR EXPERIENCES WITH THE NONSUTURE TECHNIC OF ANASTOMOSIS IN PRIMARY ARTERIAL INJURIES

CHARLES F. STEWART, M.D.

NEW YORK, N. Y.

THE PRESENT COMMUNICATION is concerned with the problem of restoring blood flow through arteries damaged by missiles. Seven cases are reported here in which a nonsuture technic was attempted. The casualties were treated in an American Evacuation Hospital in the recent European War.

As is usually the case in war-time, the desire to restore the functional continuity of arteries became to us a problem of pressing and intriguing interest. We were fortunate in having the timely advances of Blakemore, Lord and Stefko¹ as the basis for our attempts. The devices with which surgeons have tried to repair arteries have been many in the past, and it is said that every sort of tubular structure from goose quills to chicken bones has been used. During World War I Tuffier^{2, 3} had some success with a silver plated tube coated with paraffin. Makins⁴ reported some good results with this method, and one specifically through which the distal pulsations were maintained for as long as ten days. The Carrel vein graft technic^{1, 4, 5} was sometimes satisfactory in the last war, but was technically difficult, time-consuming, and very subject to thrombus formation. Direct arterial suture,^{5, 6, 7} as stated by Leriche and Werquin,⁸ is generally impossible in war wounds. It is tedious and difficult. Ragged tears and loss of substance may make even the apposition of the arterial ends impossible. Local thrombosis frequently follows the repair.²⁷ Besides these initial factors, suture is dangerous in a war wound which is left open, as hemorrhage is apt to occur. Infection is still too often present, and, finally, there may be little or no support of the vessel by healthy adjacent tissues. Mitchiner⁹ stresses the complications developing late in patients after arteriorraphy in World War I; frequently these men developed aneurysm at the site of suture. Yet when a primary artery is simply ligated, and its continuity is not restored, the extremity may be lost due to ischemia, or there may be functional limitations evident later.^{28, 30, 31}

In reviews of the subject in 1939 and 1940, Maurer,¹⁰ and Mitchiner,⁹ respectively, gave rather unhappy pictures of what could be expected in vascular surgery in battle casualties. Only under the most perfect conditions could they give any hope of preserving the function of an artery by direct suture. Yet these conditions seldom obtain in warfare, and even then may be followed by late complications. In the early part of American participation in this war, we were impressed by the unprecedented loss of limb due to ischemic gangrene. In the Tunisian campaign, 100 per cent of our cases requiring ligation of the popliteal artery came to amputation. These observations were confirmed by others,^{11, 27} and attributed to the increased explosive effect of modern missiles. It became more important than ever to find a method to save these limbs. It had to be a method which would restore arterial blood

flow, which would rarely cause thrombosis, and one that would be relatively free of the reported late complications. The nonsuture method advocated by Blakemore, and associates,^{1, 11, 12, 13, 14} seemed to fulfill the prerequisites.

Blakemore and Lord^{1, 12} at first sought a tubular structure to act as a prosthesis, and chose a Vitallium tube which could be inserted into the divided ends of the artery. This was done experimentally both with the ends of the artery sutured in continuity (Fig. 1 A), and with them distracted and ligated over the ends of the unlined tube (Fig. 1 B). The results of this method were

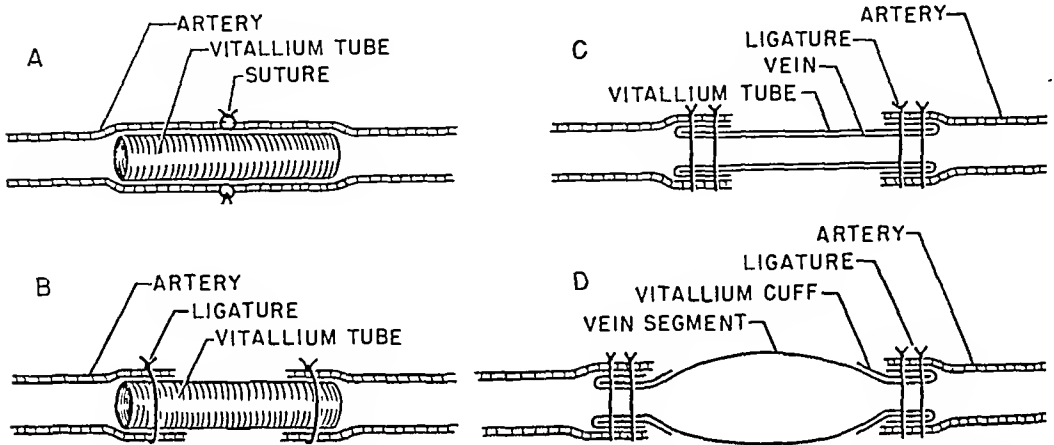


FIG. 1.—(A) Experimental: artery sutured in continuity over an unlined Vitallium tube. (B) Experimental: artery ligated over an unlined Vitallium tube with arterial ends separated. (C) Clinical: vein-lined Vitallium tube ligated in place to bridge arterial defect. (D) Clinical: vein segment reflected over Vitallium cuffs shown connecting arterial ends.

unfavorable in that only one in nine, and one out of six, respectively, were successful. Another method tried—without the use of anticoagulants—was that of reflecting the ends of the artery over metal cuffs and uniting them with a vein graft. Little success came of this plan either. The final development was the use of a Vitallium tube lined with a vein segment which overlapped the ends of the tube; this graft could be inserted into the artery with intima of vein in contact with intima of artery (Fig. 1 C). The prosthesis was held in place by two ligatures at each end. A modification of this, to bridge longer arterial defects, was the two-tube method (Fig. 1 D). In this, the vein was similarly applied, but using only a cuff of metal at either end with the interposed segment of vein not encased in metal. Both of the latter methods were highly successful experimentally, and were later applied to civilian vascular injuries, aneurysms, and other conditions, with excellent results.

We attempted the nonsuture technic in seven cases. The average time in getting these patients from the battlefield to the operating room was 12 hours and 50 minutes; the earliest one was three hours and 40 minutes. More forward installations, the Field Hospitals, devoted their time almost exclusively to critically wounded patients: Those with abdominal, chest and head wounds.

be made to reestablish functional continuity of the vessel. Ideally, an anastomosis should be done in all cases, as a limb supported only by its collateral is so frequently subject to easy fatigue, intermittent claudication, and is generally less competent than the normal one.^{28, 30, 31} In our early war experience¹¹ we were surprised at the failure to survive of many limbs in which the prognosis was thought good. It was some time after that that we acquired the metal tubes essential to the nonsuture technic. Hence, many cases went through our hands before we accumulated the experience and the material with which to try this procedure.

CASE REPORTS

Case 1.—An American soldier with two gunshot wounds, one in the abdomen and one in the left thigh. Wounded at 10:00 A. M. November 13, 1944, at Montidaly, France. On admission to our hospital, a tag of omentum was seen protruding from an abdominal wound. Both lower extremities were so cold that it was impossible to note any difference in temperature between them. A vascular injury was not seriously considered. There was no evidence of a fracture of the left femur. B.P. 90/65; P. 100.

Operation.—Major William H. Cassebaum: 4:30 P. M. November 13, 1944.

Pathology: (1) A penetrating wound of the left buttock entering the pelvis, with lacerations of the lateral wall and apex of the bladder intraperitoneally. The tract made its exit suprapubically without injury to any other abdominal viscus. There was a severe compound comminuted fracture of the left superior pubic ramus. (2) A perforating wound of the left thigh with contusion and thrombosis of the superficial femoral artery about 12 cm. below the inguinal ligament. The missile had entered posteriorly and came out anteriorly in the upper third of the thigh.

Procedure: (1) Exploratory celiotomy through a left paramedian incision, with findings as described. Closure of the two perforations of the bladder followed by cystostomy with a catheter. The left first and second lumbar sympathetic ganglia were excised. Débridement of the fractured pubic ramus was carried out. The abdominal incision was closed in two layers. (2) Débridement of wounds of the left thigh. The femoral artery was then isolated: the thrombus and clot were removed through a longitudinal incision in the artery. Damage to the intima was seen but the artery wall was sutured. When control from above was released, a little blood leaked from the arterial suture line, and in a short while the artery seemed thrombosed again. Hence, the thrombosed section was resected, together with a section of the femoral vein. An anastomosis, using the vein segment and Vitallium tube, was attempted. The lower end of the prosthesis, however, pulled out of the artery while the upper end was being inserted. As the patient's pulse was 160 at that time, it was considered unwise to persist. Both ends of the artery were ligated. The distal arterial end bled slightly before ligation. Operating time three and one-half hours. From admission to completion of operation, the patient had received 2,500 cc. of whole blood.

Course.—November 17, 1944: Considerable pain in the affected leg for past two days. The foot was obviously dead, the calf tender and tense. Sensation to pinprick was noted as dullness to within three inches of the ankle. There was no sensation in the foot. "We have not been able to restore his blood volume for fear of damaging his liver or increasing the existing jaundice, which must certainly be due to transfusions."*

* We had many reactions—jaundice, pyrexia and hemolysis—resulting from massive blood transfusions. Most of these were in Group A recipients and seemed to occur after more than 1,500 cc. of pooled plasma or Group O blood. Type specific transfusions (i.e., A donor to A recipient) completely eliminated this reaction. I hope Captain George H. Parks will report further on this subject).

PRIMARY ARTERIAL INJURIES

Second Operation.—6:00 A. M., November 17, 1944.—Guillotine amputation of the left leg below the knee. The skin and gastrocnemius muscle bled moderately; and the latter muscle was of good color. The other muscles of the lower leg were grayish-purple and did not bleed. The anterior tibial muscles were "almost white."

Case 2.—An American soldier suffering from a shell fragment wound of the left leg received at 3:00 P. M. November 13, 1944, at Leintry, France. Examination on admission revealed a patient in profound shock. B.P. 85/35; P. 120. There was a perforating wound of the right leg with entry on the medial side of the knee at the patella, with the wound of exit about four inches above the knee cap on the lateral aspect of the thigh. Only slight movement of the toes and foot was noted. A dorsalis pedis pulse was said to be perceptible on admission (this was questioned). Roentgenograms revealed a fracture of the medial condyle of the femur extending into the joint. Patient's condition was good at 10:00 P. M. 1,200 cc. of blood and 750 cc. of plasma were given preoperatively.

Operation.—Major Andrew F. McBride, 4:00 A. M. November 14, 1944.

Pathology.—Severe shell fragment wound of the right lower thigh; traumatic arthrotomy of the right knee joint, with a complete compound comminuted fracture of the medial condyle of the femur. Severance of the tibial and peroneal divisions of the sciatic nerve. Division of the popliteal artery and vein. Absent distal pulsations; the popliteal pulse was absent with the patient under anesthesia. The affected foot was cooler than the well foot and insensible to stimuli.

Procedure.—A sciatic nerve block was done first. Exploration of the popliteal space was performed through a midline incision with a tourniquet fastened on the upper thigh. The vessels and nerves were exposed and found divided at a level believed to be between the superior and inferior geniculates. The popliteal artery was damaged from 0.5 cm. to 1.0 cm. beyond each divided end, and the ends were filled with thrombus. Two attempts were made to interpose a venous transplant with two metal cuffs. The great saphenous vein was used. The lower end of the transplant was hitched up first, and with release of the tourniquet there was a steady drip of blood from the distal artery through the vein segment. The prosthesis, however, came out when connected to the proximal end of the artery. A second attempt at union was successful at both ends, but after ten minutes the arterial pulse forced the transplant from the artery. The artery was then ligated. Nothing was done to the knee joint at this time. Plaster encasement applied. A sympathectomy was not done in view of the nerve section. 1,000 cc. of blood was given during operation. The operating time was three hours and ten minutes.

Course.—The leg became progressively more necrotic and an amputation through the lower third of the right thigh was done 46 hours after the first operation.

Case 3.—A German prisoner with a gunshot wound perforating the left thigh and penetrating the right thigh. Wounded at 8:00 A. M. February 1, 1945, near Colmar, France.

Examination of the patient revealed a 1 x 1 cm. wound on the posterolateral aspect of the left thigh at the junction of the middle and lower thirds. There was a 20 x 10 cm. wound of the anteromedial surface of this thigh. An obviously severely fractured femur complicated the situation. The sensibility to pain and touch were diminished in the affected foot. This foot was cold, pale and slightly cyanotic, with no pulse palpable. Circulation was described as "almost nil," yet the foot was not dead. There was an 8 x 3 cm. wound of the right thigh.

Operation.—Captain Charles F. Stewart, 2:00 A. M. February 2, 1945.

Pathology.—There was wide destruction of the vastus medialis muscle and less marked damage to the biceps femoris and adductor magnus. A complete compound comminuted fracture of the femur was associated with this perforating wound. The superficial femoral artery had been divided about 5 cm. above adductor hiatus. Division of the femoral nerve was noted.

Procedure.—Débridement of the skin, fascia, muscles and bone. Part of the femoral

vein was resected. An anastomosis of the severed femoral artery was accomplished with Vitallium cuffs, using a segment of the femoral vein. (At first a segment of the saphenous vein was tried but was found to be too small in caliber.) A good stream of blood came through the free distal end of the vein segment with the proximal end fixed in place. Anastomosis was difficult because the cuffs slipped out of the artery both before and after they were ligated. Finally, the anastomosis was satisfactorily accomplished with a cuff 4 mm. in diameter above and one 3 mm. in diameter below. There was a palpable pulsation of the artery below the anastomosis. The completed bridge lay immediately against the fracture of the femur. The sciatic nerve was blocked under direct vision in the posterior wound. Five Gm. of sulfanilamide were placed in the wounds, which were left entirely open. The foot was warmer after operation; the calf muscles, however, were slightly firm. After the necessary manipulation of putting on a hip spica, the foot again became pale and cold. Operating time five hours.

Course.—February 2, 1945, 7:00 P. M. The left foot was warm but not as warm as the right. No feeling in the foot (nerve division and block) nor ability to move it. Temperature 102.4° F. at 4:00 P. M.

February 8, 1945: Fever, up to 101.2° F. The left foot was warm but considerably mottled and slightly bluish. No pulse palpable.

February 10, 1945: Foot warm. No pulse palpable. Could move toes moderately well. Patient evacuated to the rear February 12, 1945. Condition unchanged.

Final note: (by letter from the General Hospital to which the patient had been evacuated.) "The patient was received on February 12, 1945, in fairly good condition. The day following admission he had a small pulmonary embolus, with classical chest pain and hemoptysis. The left leg was of good color and remained so; no edema. Due to the embolus, no studies (arteriograms) were made, as you suggested. His condition was improving, but he suddenly had a large pulmonary embolus on February 26, 1945, and expired. Autopsy showed thrombosis of the left femoral artery; however, it must have remained patent for some time until collateral circulation was established because of good color and warmth of the extremity. The source of the pulmonary emboli was the left internal iliac vein. The patient's condition was never good enough to warrant examination of the wounds (hip spica) or any type of surgery."

Case 4.—An American soldier wounded at 11:00 A. M. February 5, 1945, by a shell fragment perforating the upper third of the left thigh.

On examination, the patient was found to have a 4 x 4 cm. wound on the anterior aspect of the thigh below the inguinal ligament, lateral to the femoral canal. The laceration was surrounded by a zone of swelling. The left leg and foot were quite cool, and the muscles of the thigh and leg were firm. No pulse could be felt in the foot. There was no evidence of fracture or of nerve injury. 500 cc. of plasma and 500 cc. of whole blood were given preoperatively.

Operation.—Major William H. Cassebaum. 6:00 A. M. February 6, 1945.

Pathology.—There was a thrombus in the femoral, the profunda femoral and the lateral femoral circumflex arteries. In the anterior wall of the femoral artery there was a slit a few millimeters long. The walls of the involved vessels were severely contused with resulting subadventitial hemorrhage. The wounds were very dirty.

Procedure.—The wound over the femoral artery was extended upward. A plasma tubing clamp was placed on the femoral artery proximal to the injured portion. The small slit in the femoral artery was enlarged and the thrombus and clot was removed, by milking it out from below. Some bleeding from below then became apparent, and the blood flow was controlled from below. A portion of the femoral vein was excised, reversed and transplanted into the artery after having been passed through two Vitallium tubes each about one inch long. After joining the anastomosis, no pulsation of artery distally became apparent. The wound was débrided. Little or no bleeding was encountered in the sartorius or quadriceps femoris muscle. Woolen material (clothing fragments) was removed from the wound. A considerable amount of venous bleeding was noted. After

operation the leg still appeared cold and dead. Gas gangrene was feared because of destruction to collaterals and the extensive contamination of the wound.

During operation the patient received 1,000 cc. of 5 per cent glucose in saline, and 1,500 cc. of whole blood.

Course.—February 7, 1945. 7:00 A. M. Thigh swollen and gas present.

Second Operation.—February 7, 1945. 8:45 A. M. High thigh amputation of the left lower extremity. Clot occupied the vein graft, though when this was later removed the system was patent to water from a 30-cc. syringe under pressure of the weight of the plunger.

Case 5.—An American lieutenant with a severe gunshot wound of the right thigh received at 7:30 A. M. April 8, 1945. Admitted at 5:20 P. M.

Examination.—B.P. 125/80; P. 88. The patient had a large hematoma of the right thigh with an hemarthrosis of the right knee. General condition very good. The leg was in a Thomas splint. Motion of the toes was good; posterior tibial pulse feebly palpable. 1,000 cc. of 5 per cent glucose in saline and 500 cc. of blood were given the patient prior to operation.

Operation.—Captain George Crawford. 3:30 A. M. April 9, 1945.

Pathology.—A compound comminuted fracture of the right femur with laceration of the upper third of the popliteal artery. Good pulsations of the dorsalis pedis and posterior tibial arteries were noted in the operating room, but these disappeared just before the patient was anesthetized.

Procedure.—The wound on the laterosuperior aspect of the knee was opened and large blood clots were evacuated. The surrounding muscle was infiltrated with clotted blood. In its superior portion the knee joint had been pierced. Irrigation of the knee joint with saline was followed by the instillation of 10,000 U. of penicillin and closure of the capsule. On evacuation of blood clot from the thigh wound profuse hemorrhage was encountered; hence, the popliteal artery and vein were exposed. An incomplete tear was found in the upper third of the popliteal artery. The tear measured 2 cm. in length and encompassed two-thirds of the circumference of the vessel. A section of the popliteal vein was taken, threaded through a cannula which was placed in the torn popliteal artery. Upon release of the tourniquet, and after dissecting the adventitia off the superior end of the artery, a pulsation was felt in the distal segment. Sulfanilamide powder was dusted into the wound. A Tobruk splint was used. A right paravertebral sympathetic block was done with 2 per cent novocaine. The foot was warm and of good color after the operation.

Course.—April 10, 1945: Foot warm and of good color but no palpable pulse.

April 11, 1945: Pentothal anesthesia; wound inspected. The popliteal artery was palpated. A definite pulsation was palpable below the anastomosis. Tobruk splint replaced by a plaster hip spica.

April 14, 1945: Good dorsalis pedis pulse palpable.

Case 6.—An American soldier suffering from a penetrating shell fragment wound of the right arm received at noon on April 25, 1945. He was admitted to this hospital at 6:45 P. M. On examination, a penetrating wound of the lower third of the lateral side of the right arm was seen; in the anterior axillary fold the skin had been torn slightly and the foreign body lay in the right pectoral muscles. No pulse was palpable in the right wrist and there was paralysis of the three major nerves. B.P. 120/60; P. 120. The forearm and hand were pale but not cold. The fingers were flexed and stiff. Some capillary circulation was thought to be demonstrable.

Operation.—Captain Edmund R. Taylor and Captain Charles F. Stewart. 10:20 P. M. April 25, 1945. B.P. 116/82; P. 138.

Pathology.—Wound as described, with severe damage to the triceps muscle. A compound comminuted fracture of the midthird of the humerus was revealed. The brachial artery was completely severed just below the origin of the profunda brachial artery. A profuse blood flow came from the distal end of the artery. In addition, the brachial vein

was lacerated. The radial nerve had been completely divided and its ends were frayed for 6 cm. on each side. The median nerve was 30 to 50 per cent divided. Although the ulnar nerve was not functioning, it was thought to be anatomically intact. The profunda brachial artery was divided at the site of the fracture.

Procedure.—Débridement of the wound tract and curettage of the fracture ends. An anastomosis was carried out using a segment of the brachial vein and two Vitallium cuffs. After several attempts to insert a 3-mm. cuff at each end, a 2-mm. cuff had to be used at the lower end. No pulsation in the distal segment could be palpated at the termination of the procedure. All nerves in the wound were injected with 2 per cent novocaine; these were the radial, the musculocutaneous, the median and the medial anti-brachial cutaneous nerves. The radial nerve ends were each transfixed, though separated, with a fine wire suture. A shoulder spica was applied. During operation the patient received 1,500 cc. of blood.

Course.—5:45 A. M. April 26, 1945: Cervical sympathetic block, right, with 5 cc. of 2 per cent novocaine. Heparin therapy was started by continuous intravenous drip—the patient receiving 20 cc. of heparin solution in 2,000 cc. of diluent in 24 hours.

10:40 A. M. April 27, 1945: Cervical sympathetic block. Fingers less stiff and cold. In sitting position, the hand veins distended and the color of the hands became pinker. The forearm was warmer and less tense.

6:00 P. M. April 28, 1945: Cervical sympathetic block with 20 cc. of 1 per cent novocaine. Resulting Horner's syndrome. Right hand was mottled and cold. The fingertips were quite blue.

April 29, 1945: Cervical sympathetic block. No change in hand.

April 30, 1945: Hand definitely gangrenous with a line of demarcation at the wrist.

Because of the tactical situation, the patient was evacuated to a General Hospital without his hand being amputated, though it was inevitable.

Case 7.—An American soldier with a gunshot wound of the left thigh incurred at 9:20 A. M. June 18, 1945, at Augsburg, Germany, when the patient was accidentally shot by another soldier. On examination, there was a perforating wound of the lower third of the left thigh. No pulse was felt in the foot, but the foot was warm. Motion of the foot was normal.

Operation.—Major Edgar L. Frazell. 1:00 A. M. June 19, 1945.

Pathology.—There had been considerable bleeding into the muscle planes. The superficial femoral artery, about 1.5 cm. proximal to the superior internal geniculate artery, was 50 per cent divided. The proximal and distal lumina were filled with soft blood clot. Both ends bled on removal of the clot.

Procedure.—The artery was approached from the posteromedial aspect, following the tract of the missile. A plastic tube without a vein-lining was used to bridge the defect, as much of the lateral wall was missing. The prosthesis was sutured (ligated) into place, and the lacerated vessel wall was partially approximated. There was a questionable dorsalis pedis pulse after the completion of the operation. Heparin was started: 30 cc. in 1,000 cc. of saline was given in the first 24 hrs. The sciatic nerve was blocked with novocaine.

Course.—Ten hours postoperatively: The left foot was warm and capable of motion. The posterior tibial pulse was definitely palpable. Blood coagulation time 60 minutes plus.

One week postoperatively: The left foot was warm, viable, and the pulses were easily palpable in the foot. Mild wound infection. Secondary closure of the wound was accomplished on the 14th day. Three weeks postoperatively, with wounds healed, palpable pulses and functioning toes, the patient was evacuated to the rear.

GENERAL DISCUSSION.—Seven cases of arterial injury with attempted nonsuture anastomosis have been presented. These are representative vascular injuries, demonstrating division of the artery in three cases, thrombosis in two,

PRIMARY ARTERIAL INJURIES

and lateral laceration in two. The limbs of three of these patients survived. Two of the satisfactory results were obtained with vein-lined tubes (Cases 3 and 5), while the third was accomplished with an unlined tube of plastic material (Case 7).²⁹ Of the failures, the limb in one patient (Case 4) was probably not viable at the time of operation. Two other patients had their arteries ligated after failure of efforts to insert the prosthesis. The remaining case was treated with a prosthesis which was certainly too small.

Three successes in seven attempts makes a survival rate of 43 per cent in this group. All seven cases had severe vascular injuries. It is impossible to state which of these limbs might have survived with ligation alone. All three of the satisfactory cases might have retained a viable extremity without restoration of continuity of the vessel. In Case 6, the loss of limb with ligation alone could have been predicted. Because of the inability to predict survival of limb in all cases of interruption of flow in primary artery injuries, it is safer to insert a prosthesis where possible. Comparison of statistics in so small a series is futile, but for general interest the results of our major vascular surgery in the first half of 1945 may be included. (Dr. Andrew F. McBride will publish later a more complete analysis of all of our vascular cases.) Excluding injuries to any except major arteries, and five of the cases described, our records in 1945 show these results:

Artery Ligated	No. of Cases	No. Amputated	% of Limb Survival
Common femoral.....	1	1	0
Superficial femoral.....	14	6	57
Popliteal.....	8	8	0
Axillary.....	2	1	50
Brachial.....	8	1	88

In 1944, the leg survived in only 25 per cent of 16 cases of ligation of the superficial femoral artery, and the limbs in 25 per cent of 12 ligated popliteal arteries survived.

Breaking our seven cases down into location and result, we have:

Artery Involved	No. of Cases	No. Amputated	% of Limb Survival
Common femoral.....	1	1	0
Superficial femoral.....	3	1	67
Popliteal.....	2	1	50
Brachial.....	1	1	0

When the prosthesis cases are included with the general data for the half-year period, the results are:

Artery Involved	No. of Cases	No. Amputated	% of Limb Survival
Common femoral.....	2	2	0
Superficial femoral.....	16	6	63
Popliteal.....	9	8	11
Axillary.....	2	1	50
Brachial.....	9	2	78

Cases 1 and 2 resulted in amputation. Neither of these cases had a prosthesis inserted, merely attempted. Since they were done in 1944, they are not

included in the last table. Inclusion of the prosthesis cases in the statistics for 1945 raises the survival of limbs in superficial femoral artery cases from 57 to 63 per cent, and in the popliteal group from 0 to 11 per cent. Brachial artery statistics fall from 88 to 78 per cent, with the failure of one prosthesis case.

Our difficulties with the nonsuture vein graft technic become apparent from a study of the cases presented. A working knowledge of the method from previous experience or experimental work would have been of great help to us. The crucial and most difficult step in the procedure is the actual insertion of the prosthesis into the artery. Failure in Cases 1 and 2 was due to this factor. It is believed that failure in Case 6 was due to the use of too small a prosthesis. Blakemore²⁶ recommends the following technic for inserting the prosthesis: (1) Mosquito clamps are attached to the artery end at three or four points. The bite of the clamp includes all layers of the arterial wall for a distance of 1 to 2 mm. Care must be exercised not to tear the thickened, contracted arterial wall. (2) Assistants hold the mosquito clamps, slightly everting the edges of the artery. (3) The operator holds the bare rim of the vein-covered metal cuff in a hemostat. While the loose end is held taut to thin-out the vein, the operator pushes the prosthesis into the end of the artery. Doctor Blakemore recommends that steady constant pressure for a minute or more be exerted while inserting the cuff. This exertion is necessary to overcome the spasm of the arterial wall. Blakemore and Lord have observed a sudden release of spasm during this maneuver, allowing the cuff to slip into the artery. It can be compared to overcoming spasm by steady traction in reducing a dislocated shoulder.²⁶ In some of our cases, seen long after injury, the arterial spasm seemed almost irreversible. Use of too small a prosthesis, or tearing of the artery wall was apt to result in such cases. To overcome the strong spasm of an artery, dilatation with a small speculum might be of value. Such a speculum should be inserted only 2 to 3 mm. lest the intima be damaged beyond the distance of contact with the prosthesis. The speculum should be used as a very gradual dilator, and should be removed before attempting to insert the prosthesis. Certainly, in the light of present knowledge, preoperative nerve blocks and periarterial stripping^{6, 8, 10} should be used in an attempt to dilate the affected artery.

Anastomosis by the described technic requires the lumen of the artery to be impinged upon, or narrowed by, three foreign layers of material. These are the Vitallium tube and two layers of the vein graft. When the vein segment is too large in circumference for the caliber of the cuffs, there will be a certain amount of pouting of the vein wall into the lumen of the prosthesis. This may be enough to be obstructing. To remedy this fault, a vein segment of the appropriate caliber must be used. It should be pulled taut in all axes. A piece of vein that is too small in caliber is equally unsatisfactory. In Case 3 a segment of saphenous vein was prepared for a superficial femoral anastomosis. When taken, this segment was in spasm, and could not be dilated or relaxed enough to provide an adequate lumen. A femoral vein graft was finally used. The required length of any vein transplant is surprisingly great. Doctor Blake-

more²⁶ has arrived at this method of estimating the length of the vein segment needed: (1) The severed arterial ends are grasped with clamps, as described above, and drawn together with "physiologic" tension (*i.e.*, the degree of tension which would seem compatible with the normal elasticity of the vessel). (2) The resulting gap between the ends of the artery is then measured. (3) To the measured distance is added 2 cm. to allow for the length of the vein graft investing the cuffs. This computation gives the total length of the vein segment needed. The tension exerted on the inserted vein graft by the normal elastic retraction of the arterial ends decreases the opportunity for pouting and redundancy of the vein graft within the cuffs. Care, of course, must be exercised to install the vein graft in the reverse of its normal axis, allowing the blood to pass any valve that might be in the segment. A functioning valve would doom the procedure.

Extrusion of the prosthesis from the arterial lumen was the reason for failure in Case 2. The causes of this accident are several. First, as noted above, the introduction of this type of prosthesis considerably reduces the area of the arterial lumen, and does so abruptly. Naturally, the blood pressure against this partially obstructing device is great. Added factors, such as pouting of the vein and too small a prosthesis, may increase this hazard. Secondly, the low, rounded ridges on the cuffs may be inadequate to hold the ligature. It would seem preferable if these ridges, while low, could be sharply angulated on the side against which the ligature would rest. Finally, ligation is not sufficiently tight when such an accident occurs. The use of the surgeon's knot, when tying over the inelastic cuff, would seem to be the most dependable procedure.²⁶

Mann, *et al.*,¹⁸ report that the internal diameter of an artery may be reduced 70 per cent before there is a 50 per cent reduction in blood flow. What the effects of such a reduction of flow are on coagulation, and on the function of the part, is only conjecture. Thrombosis is a threat in all vascular surgery. The eddying of the stream of blood even around an intima-lined connection probably increases the likelihood of thrombus formation. This would be particularly true when the prosthesis is small. Careless handling of the vein segment and of the arterial ends increases the danger of coagulation. The utmost delicacy must be used in handling these structures. Heparin, or dicoumarol, should be used in all cases.^{23, 25} Heparin did not become available to our hospital until the Spring of 1945, and then in only very limited quantities. As a result, only the last two cases in our series had the benefit of the drug. Its use in such a small group cannot be adequately evaluated. Undoubtedly an anticoagulant offers far greater chance of success. Now that the subcutaneous administration of heparin in Pitkin's menstruum has been developed,²⁵ a great chore has been removed from the postoperative care.

Gas gangrene and hemorrhage, the other principal complications, have been mentioned. Blakemore, and his colleagues, have not been troubled by secondary bleeding. Their technic, as shown by excised specimens, leads to firm union between artery and vein segments.

The time between injury and operation will doubtless seem long to many, but these were the existing conditions. At times the volume of work was overwhelming. During one advance, the time from the patient's admission until he could be operated upon (the "surgical-lag") was 54 hours! None of the cases presented was treated during that time.

The composition of the tube used in Case 7 is not known. It has been suggested that it may have been a polyvinyl acetate plastic. It seems to have been highly satisfactory. The tube was flexible; in hot water it was easily malleable and ridges were moulded on it before its use. The material was almost completely transparent, slightly opalescent.²⁹ Of course, the conditions for its use were good, for the vessel was incompletely divided and was partially sutured. What if the arterial ends are simply pulled over the ends of the tube and ligated in distraction? Does not the ligature cause necrosis and cut through the vessel wall leading to late hemorrhage? Would this not be particularly to be feared in a gaping wound where the prosthesis had little outside support? Temporary use of such a tube is plausible. That is the way in which Tuffier's tube came to be used in the last war,^{3, 4} and the Canadians in this war were using a glass tube in the same way.^{19, 20} Perhaps the plastic tube has further possibilities where anticoagulants are used in conjunction. It is quicker and easier to insert, and has not the necessary encroachment upon its lumen by a thickness of vein. Certainly, however, the vein-lined tube is more physiologic, and, when the technical difficulties of insertion are lessened, approaches the ideal alluded to by Leriche and Werquin.⁸

CONCLUSIONS

The nonsuture method offers new hope in the treatment of vascular injuries, and should be attempted when the limb is in danger of ischemic gangrene.

An outline of ideal treatment of a case with a lacerated, divided or thrombosed artery might be as follows:

I. Preoperative:

1. Shock treatment: morphine to allay pain. Papaverine is theoretically good in vascular cases, but not without danger.²⁴ Transfusions with type specific blood to restore blood volume; this should be controlled by hematocrits, and blood and plasma specific gravity determinations.

2. Prophylactic treatment: antitetanic toxoid or serum with polyvalent gas gangrene serum if the conditions indicate it. Penicillin should be used to counteract wound infection.

3. A sympathetic nerve block should be done on the affected side.

II. Operation:

1. Wide and thorough débridement of the wound.

2. Clean isolation of the vessels involved and temporary local occlusion of the artery with rubber guarded clamps.

3. A cursory examination of the collateral circulation which will give an idea of its ability to support the limb. (See page 3).

PRIMARY ARTERIAL INJURIES

4. Preparation of the prosthesis of adequate size from the adjacent vein, being sure to reverse it and to keep one end marked. (Use of a preserved vein transplant would facilitate and speed the procedure.¹²)

5. Débridement of the ends of the artery and periarterial stripping one inch away from the divided ends.

6. Removal of all clot from the vessel ends and irrigation of them with a heparin-saline solution.

7. Insertion of the largest-sized prosthesis that can be used, starting the procedure with the upper end of the artery, and releasing the upper clamp to be sure of the flow through the prosthesis.

8. Firm double ligation of the arterial ends over the prosthesis with heavy silk.

9. Release of the occluding clamps.

10. Closure of the vascular sheath and wound whenever possible.

11. Local block of the nerves of the involved limb may prove helpful.

III. Postoperative Care:

1. The blood volume should be kept up with whole blood transfusions as indicated.

2. Penicillin, or chemotherapy,¹³ should be continued.

3. The patient should be heparinized by subcutaneous injection of the drug in Pitkin's menstruum.^{20, 21, 25} Heparinization includes controlling the coagulation time by adequate measures.

4. Repeated nerve blocks should be given as long as the state of the circulation is in doubt.

5. The extremity should be splinted in a neutral position for ten to 14 days.^{6, 9}

6. The limb should be maintained at a subnormal temperature.²²

SUMMARY

(1) Seven cases with gunshot or shell fragment wounds of major arteries are presented. In all of these vessels a nonsuture anastomosis was attempted with varying results.

(2) A discussion of technical difficulties and possible improvements follows.

(3) The paper is concluded with a plan of ideal treatment of such cases.

REFERENCES

- ¹ Blakemore, A. H., Lord, J. W., Jr. and Stefkó, P. L.: *Surgery*, 12, 488, 1942.
- ² Tuffier, M.: *Bulletin de l'Académie de Médecine de Paris*, October, 1915, 455.
- ³ Tuffier, M.: *Bulletin et Mémoires de la Société de Chirurgie de Paris*, 43, 1469, 1917.
- ⁴ Makins, G. H.: *Gunshot Injuries to the Blood Vessels*. John Wright and Son, Ltd., Bristol, England. 1919.
- ⁵ Pratt, G. H.: *Surgical Clinics of North America*. April, 1943, 358.
- ⁶ Holman, E.: *Surgery, Gynecology and Obstetrics*, 75, 183, 1942.
- ⁷ Elkin, D. C.: *ANNALS OF SURGERY*, 120, 284, 1944.
- ⁸ Leriche, R., and Werquin, M. G.: *Lancet*, 2, 296, 1940.
- ⁹ Mitchiner, P. H.: *St. Thomas' Hospital Gazette*. London, 38, 92, 1940.
- ¹⁰ Maurer, M. A.: *Bulletin et Mémoires de l'Académie de Chirurgie de Paris*, 65, 1156, 1939.

- ¹¹ Blakemore, A. H., and Lord, J. W., Jr.: *Journal of the American Medical Association*, 127, 685, 1945.
- ¹² Blakemore, A. H., Lord, J. W., Jr., and Stefko, P. L.: *ANNALS OF SURGERY*, 117, 481, 1943.
- ¹³ Blakemore, A. H., and Lord, J. W. Jr.: *Archives of Surgery*, 47, 352, 1943.
- ¹⁴ Blakemore, A. H., and Lord, J. W., Jr.: *Journal of the American Medical Association*, 127, 748, 1945.
- ¹⁵ Bird, C. E.: *Surgery, Gynecology and Obstetrics*, 60, 926, 1935.
- ¹⁶ Gage, M., and Ochsner, A.: *ANNALS OF SURGERY*, 112, 938, 1940.
- ¹⁷ Churchill, E. D.: *ANNALS OF SURGERY*, 120, 268, 1944.
- ¹⁸ Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J.: *Surgery*, 4, 249, 1938.
- ¹⁹ Personal communication.
- ²⁰ Walker, J., Jr.: *Surgery*, 17, 54, 1945.
- ²¹ Loewe, L., and Rosenblatt, P.: *American Journal of Medical Sciences*, 208, 54, 1944.
- ²² Brooks, B., and Duncan, G. W.: *ANNALS OF SURGERY*, 112, 130, 1940.
- ²³ Murray, G. D. W., and Best, C. H.: *ANNALS OF SURGERY*, 108, 163, 1938.
- ²⁴ Sagall, E. L., and Dorfman, A.: *New England Journal of Medicine*, 233, 590, 1945.
- ²⁵ Loewe, L., Rosenblatt, P., and Hirsch, E. *Journal of the American Medical Association*, 130, 386, 1946.
- ²⁶ Blakemore, A. H.: Personal communication.
- ²⁷ Rose, C. A., Hess, O. W., and Welch, C. S.: *ANNALS OF SURGERY*, 123, 161, 1946.
- ²⁸ Crutcher, R. R.: *ANNALS OF SURGERY*, 123, 304, 1946.
- ²⁹ DeBakey, M. E., and Simeone, F. A.: *ANNALS OF SURGERY*, 123, 534, 1946.
- ³⁰ Bigger, I. A.: *Archives of Surgery*, 49, 170, 1944.
- ³¹ Tyson, M. D., and Gaynor, J. S.: *Surgery*, 19, 167, 1946.

PHENYLPROPANOLAMINE HYDROCHLORIDE.*
A VASOPRESSOR DRUG,
FOR MAINTAINING BLOOD PRESSURE DURING
SPINAL ANESTHESIA

PAUL H. LORHAN, M.D., AND DONN MOSSER, M.D.

KANSAS CITY, KANSAS

FROM THE UNIVERSITY OF KANSAS HOSPITALS, DEPARTMENT OF ANESTHESIOLOGY, KANSAS CITY, KANSAS

THE USE OF PRESSOR AGENTS for the prevention or alleviation of the fall in blood pressure which frequently accompanies spinal anesthesia has become an accepted and very useful practice. A new agent which holds promise of combining in considerable measure the desirable features and minimizing the undesirable properties of these agents, deserves extended clinical evaluation as a potentially very useful agent for this purpose. This is more apparent if one considers briefly the individual pharmacologic characteristics of related compounds.

Whereas epinephrine has the greatest effect on blood pressure of any of these agents; however, its effect is relatively evanescent and is apt to be followed by a short period of hypotension after the pressor response to epinephrine has subsided.

It is particularly noteworthy that with an elevation of the systolic pressure, there is always a decrease in the diastolic pressure and the peripheral vascular resistance.

Epinephrine lacks the property of stimulating the respiratory center and has no appreciable direct effect on the respiratory rate as is seen with ephedrine. When it is given intravenously an apnea may follow due to the reflex inhibition of respiration caused by the increased pressure in the carotid sinus and cardio-aortic area. The pulse rate at the height of the rise is accelerated at first, followed by a bradycardia.

Upon the central nervous system epinephrine has very little stimulating effect. Nevertheless, restlessness, apprehension, headache, and tremor may occur in some individuals.

Epinephrine stimulates the heart by a direct effect on the myocardium and the conduction tissue. In the presence of other factors affecting cardiac irritability, such as cyclopropane or ether anesthesia; epinephrine is particularly likely to precipitate abnormal ventricular rhythms.

Successive administration of the same dose of epinephrine will produce equipressor responses in contrast to repeated doses of ephedrine.

As compared to epinephrine, ephedrine has a relatively low order of

* Phenylpropanolamine hydrochloride is distributed under the name of "Propadrine" hydrochloride; and the material used in this study was provided by the Medical Research Division, Sharp & Dohme, Inc., Philadelphia, Pennsylvania.

pressor activity but the duration of its action is very much longer than that of epinephrine. Its pressor effect is not followed by an hypotension following a single dose, as is seen with epinephrine. Repeated usage of ephedrine at frequent intervals will ultimately produce a myocardial depression. This factor necessitates using it with caution in patients with cardiovascular disease.

Upon the pulse rate a bradycardia usually occurs at the height of the blood pressure response.

Ephedrine stimulates the respiration, whereas epinephrine and neosynephrine usually will produce an "apnea." Ephedrine will increase the respiratory minute volume by approximately 20 per cent.

Upon the central nervous system ephedrine acts as a stimulant and frequently patients under a spinal anesthetic will experience variable degrees of nervousness, palpitation, sweating and marked precordial pain.

Neosynephrine has proved to be a useful drug in sustaining blood pressure. Its pressor effect is greater than that of ephedrine but its duration of action is not as long.

The pharmacologic actions of neosynephrine are similar to those of epinephrine and ephedrine. The blood pressure is raised within a few minutes after injection, reaching a peak and then gradually tapering off to a normal level. Its vasopressor effects last about five times as long as epinephrine and slightly less than ephedrine. It acts principally by peripheral vasoconstriction and slightly by cardiac stimulation. By compensatory reflexes or direct action on the sino-auricular node it slows the heart rate below normal, so that the ensuing bradycardia may become alarming at times. Accompanying the bradycardia there is a marked dilatation of the heart. Cardiac arrhythmias occur infrequently, and central nervous stimulation is absent.

As will be noted, all three sympathomimetic drugs possess some disadvantages, so that the introduction of a new vasopressor possessing qualities similar to the above agents but with the elimination of the undesirable effects is always welcome.

Phenylpropanolamine hydrochloride was first found by Chen, and his associates,¹ to have a greater pressor effect than ephedrine with the same duration of action. The compound does not possess the action of epinephrine in potentiating cardiac irritability. Unlike ephedrine it does not produce undesirable stimulation of the central nervous system. The properties of prolonged pressor activity unaccompanied by cardiac excitation or a secondary fall in blood pressure without central nervous system stimulation combine to make this a most useful compound. Because phenylpropanolamine hydrochloride offered great promise of overcoming certain disadvantages noted with other agents we have undertaken to evaluate it in a group of 263 patients who have undergone a total of 280 operations (Table I).

Spinal anesthesia was administered for all procedures, novocaine and pontocaine being the anesthetic agents used. The dosages of novocaine ranged from 35 to 120 mg., and of pontocaine from 8 to 20 mg. The level of anesthesia was determined by the type of surgery contemplated, but the eighth

PHENYLPROPANOLAMINE HYDROCHLORIDE

TABLE I

Abdominal Surgery:	
Stomach: (gastrectomy, gastro-enterostomies, gastrostomies, perforations repair).....	13
Intestinal: (enterostomy, ileostomy, obstruction)	7
Gallbladder: (cholecystectomy, exploration of ducts, cholecystogastrostomy).....	8
Pancreas: (resection of, pancreaticojejunostomy).....	2
Appendix: (appendicectomy)	10
Colon: (colostomy, repair of colostomy, resection of, combined abdominal-perineal).....	27
Herniae: (ventral, femoral, inguinal, perineal, incisional).....	46
Explorations.....	6
Miscellaneous.....	10
Total.....	129
Urologic Surgery:	
Transurethral procedures: (cystoscopy, pyelograms, manipulation of stones).....	39
Prostatic resections: (transurethral).....	43
(Suprapubic).....	14
(Perineal).....	5
Bladder: (cystostomy, exploration).....	10
Kidney: (nephrectomy, nephrolithotomy).....	13
Miscellaneous.....	9
Total.....	133
Gynecologic Surgery:	
Hysterectomy: (abdominal, supravaginal, vaginal).....	10
Perineorrhaphy.....	3
Miscellaneous.....	4
Total.....	17
Orthopedic Surgery: Total.....	2

dorsal segment was the usual level for lower abdominal surgery and the fourth dorsal segment for surgical intervention in the upper abdomen. Preoperative medication differed in no way from that customarily administered.

Since it was the object of this investigation to determine the influence of phenylpropanolamine hydrochloride on the blood pressure in the presence of a spinal anesthetic it was necessary to establish the average effective dose of the drug. During early phases of the work, doses as small as 15 mg. were used but were found to be inadequate. After further study with increasing amounts of the drug a consistent and reproducible response was evoked with 50 mg. (1 cc.). The mode of administration by intramuscular injection differed in no way from that employed with similar preparations.

Patients to whom fluids have been administered parenterally either during or after operation were excluded from this study as unsuited to its purpose since such measures would undoubtedly influence blood pressure and render difficult an assessment of the true rôle played by phenylpropanolamine hydrochloride in maintenance of the preoperative blood pressure level.

The time of administration of the drug, as related to the anesthetic agent, is presented in Table II. In the majority of the cases a pressor effect was observed almost immediately following administration, with the blood pressure reaching its maximum response usually within ten minutes.

To evaluate the effectiveness of the drug in maintaining blood pressure it was necessary to establish certain arbitrary criteria. A response was regarded

as "satisfactory" if the systolic pressure did not fall more than 10 per cent below, nor rise more than 25 per cent above, the preoperative level. Such a "satisfactory" response occurred in 263 cases, and in 22 operative cases a fall in blood pressure was noted. It should be observed that nine of these 22 patients had preoperative systolic pressures over 160 millimeters of mercury, and two of the nine received phenylpropanolamine hydrochloride in dosages which, judged by later experience, were inadequate. In the remaining seven

TABLE II

TIME OF ADMINISTRATION OF PHENYLPROPANOLAMINE HYDROCHLORIDE

Prior to administration (by 5-10 mins.)	223
Simultaneously with administration of spinal anesthetic	50
After administration of spinal anesthetic	7
Total	<hr/> 280

TABLE III

AGE DISTRIBUTION

	Male	Female	Total
10-19	5	2	7
20-29	9	10	19
30-39	15	15	30
40-49	13	25	38
50-59	30	10	40
60-69	57	16	73
70-79	46	2	48
80-89	7	0	7
90-99	1	0	1
Total	<hr/> 183	<hr/> 80	<hr/> 263

TABLE IV

PREOPERATIVE BLOOD PRESSURE FINDINGS

Hypertension:		
(systolic pressure over 160 mm Hg)	17 cases	
Normal pressure:		
(systolic pressure from 90-160 mm Hg)	243 cases	
Hypotension:		
(systolic pressure below 90 mm Hg)	3 cases	
Total	<hr/> 263 cases	

the preoperative blood pressure level was not maintained though each had received 50 mg. of the drug.

An excessive rise in blood pressure is as undesirable as a fall. An elevation of pressure in excess of 25 per cent of the preoperative systolic level was viewed with disfavor. Such a rise occurred in five patients, in three of which the systolic blood pressure rose above 200 millimeters of mercury. It seems worthy of comment that two of these three patients had initial pressures above 160 millimeters of mercury; in the third, the blood pressure had been normal. Nevertheless, in the majority, phenylpropanolamine hydrochloride controlled the

blood pressure very satisfactorily, maintaining the pressure at the preanesthetic level in 90 per cent of the patients studied.

With respect to age, the patients included in this series ranged from 10 to 95 years, and 49 per cent were over 60 years of age (Table III). The pre-operative blood pressure findings, roughly classified, are presented in Table IV. It will be appreciated that the age distribution of the patients necessitated rather liberal interpretation of the significance of preoperative blood pressure readings, so-called "normal" blood pressure being considerably higher for advanced age-groups than the commonly accepted standard.² Age also accounts, in large part, for the cardiovascular abnormalities noted in Table V. In view of the lack of homogeneity in this series, and the large proportion drawn from the advanced age-group, it seems fair to say that at least some of the failures with phenylpropanolamine hydrochloride could be explained on the basis of the preëxisting status of the patients treated.

In Table VI the duration of the pressor effect from a 50 mg. dose of phenylpropanolamine hydrochloride has been tabulated in 15-minute intervals,

TABLE V

CARDIOVASCULAR ABNORMALITIES PRESENT PREOPERATIVELY

Cardiac weakness (dyspnea on exertion, pitting edema of ankles).....	5
Arteriosclerotic heart disease.....	12
Arrhythmia.....	6
Hypertensive heart disease.....	18
Coronary disease.....	7
Heart block.....	2
Cardiac decompensation in the preoperative period.....	5
Aortic stenosis.....	1
Rheumatic heart disease.....	6
Aortic aneurysm.....	1
Total.....	63

TABLE VI

DURATION OF PRESSOR RESPONSE WITH A 50-MG. DOSE OF PROPADRINE HYDROCHLORIDE

Time in Minutes	Male	Female	Total
0-15	9	2	11
16-30	33	8	41
31-45	57	11	68
46-60	8	10	18
61-75	5	7	12
			150

from which it is clear that elevation of blood pressure was sustained for as long as 75 minutes after administration, with an average duration of 45 minutes.

The pulse rate remained essentially unchanged, the preoperative rate being maintained in by far the majority of the patients in this series. A slowing of the pulse occurred in 38, and an increase in eight. The criterion on this point was the following: The pulse rate was regarded as unchanged if the rate did not increase or decrease more than 10 per cent of the original rate. In many

cases the character of the pulse, as determined by palpation at the wrist, appeared to be improved.

Eight patients with previously normal heart action developed extra systoles during the preoperative and postoperative periods; pulsus alternans occurred in one of these, and partial heart block in another. A simple tachycardia was observed in 19 instances, some apprehension and nervousness was complained of by three patients, nausea was encountered in three, and cardiac pain in three others. Since 49 per cent of the patients in this series were over 60 years of age and cardiovascular abnormalities were present in 25 per cent, there would appear, prior to treatment, to be no reason to attribute the cause of these developments in the cardiovascular system to the compound. This is especially true since it is extremely difficult to distinguish the possible effects of surgery and of a spinal anesthetic from those produced by phenylpropanolamine hydrochloride. Its use in this series of unselected cases subjected phenylpropanolamine hydrochloride to a relatively severe test in an effort to establish its safety and effectiveness, particularly from the cardiovascular standpoint. The type of surgical procedure carried out, the use of spinal anesthetic agents, and the age distribution of the patients, with practically half in the advanced age group, constituted a combination of factors, each of which has a marked influence upon the cardiovascular status. But even if it is assumed that the vasopressor drug used contributed to all the adverse reactions that occurred, the record of phenylpropanolamine hydrochloride would still be extremely good.

SUMMARY AND CONCLUSIONS

Phenylpropanolamine hydrochloride was used in 263 patients subjected to 280 operations after the administration of a spinal anesthetic. The ability of phenylpropanolamine hydrochloride to maintain blood pressure during the performance of a variety of surgical procedures has been established. The drug is an effective vasopressor agent with a moderately prolonged action—45 minutes—and has no apparent harmful side-effects. The optimal effective dose of phenylpropanolamine hydrochloride was found to be 50 mg. administered intramuscularly, and this dose maintained the blood pressure at preoperative levels in 90 per cent of the patients studied. From our experience with other vasopressor drugs, it would appear that phenylpropanolamine hydrochloride has a vasopressor effect which compares very favorably with the action of epinephrine, ephedrine and neosynephrine and offers certain advantages over them, namely, a more prolonged action without either the sharp rise or fall of blood pressure which usually follows the administration of epinephrine; a more prolonged action than that of neosynephrine, and less frequent excitation, than encountered with ephedrine.

REFERENCES

- ¹ Chen, K. K., Wu, C. K., and Henriksen, E.: Relationship between Pharmacological Action and Chemical Constitution and Configuration of the Optical Isomers of Ephedrine and Related Compounds. *J. Pharmacol. and Exper. Therap.*, 36, 363, 1929.
- ² Mosenthal, Hermon O.: In Nelson Loose-Leaf Medicine, 4, 645.

THE EFFECT OF THE LOCAL REDUCTION OF TEMPERATURE ON SCALD BURNS IN THE RAT*

HAMILTON BAXTER, M.D., AND ROBERT H. MORE, M.D.

MONTREAL, QUEBEC

FROM THE DEPARTMENTS OF SURGERY AND PATHOLOGY, ROYAL VICTORIA HOSPITAL, AND
MCGILL UNIVERSITY, MONTREAL, QUEBEC

IN SPITE of the increasing interest in hypothermic therapy in a variety of conditions,¹⁻⁵ only a few investigators have studied the effects of *local* hypothermia on the healing of thermal burns.⁶

Fay,⁷ and Allen, Crossman and Safford⁶ state that hypothermia of burned areas results in decreased pain, edema, exudation, infection and tissue damage. They also report that the burns treated by local cooling heal with a pliable scar and without much contracture. Fay does not state the basis for his conclusions but Allen, Crossman and Safford report three cases of thermal burns treated by the local application of ice bags, which were gradually withdrawn during the first week. Their impression was that these burns improved more rapidly than had occurred in their experience when burns were not cooled. In the few cases treated by these investigators, controls were apparently not used. The effect of general cooling in burn and/or traumatic shock has been studied experimentally by Blalock,⁸ Sellers and Willard,⁹ Elman, *et al.*,¹⁰ and others. Rose¹¹ has described the clinical application of cooling burned patients by placing them in a tub of water at temperatures of 70°F. On the other hand, so far as we are aware, there are no reports in the literature of experimental work where the effect of the local application of reduced temperatures on thermal burns has been studied over an extended period of time, with the object of examining the effect of hypothermia on the reparative processes. Recently, Large and Heinbecker¹² have reported that the healing of experimental wounds is delayed by local cooling and that the amount of lag is proportional to the length of the cooling period. However, Sano and Smith¹³ have shown that under reduced temperatures, fibroblasts in tissue culture formed smaller, more compactly placed cells with less intercellular material than tissue cultures of fibroblasts at 37.5°C. They believed, on the basis of these observations, that granulating surfaces so treated would have finer and less retracted scars. They decided that the optimum temperature was between 25° and 30°C. Nemoto¹⁴ has stated that while maximum growth of fibroblasts cultured *in vitro* occurs at 39°C. the rate diminished with decrease in temperature until no growth occurs at 20°C. Because of these rather conflicting observations, the prevalence of burns in modern warfare, the great variety of therapeutic agents used in their treatment, and the frequently poor cosmetic and functional results obtained in the treatment of burns, especially of the face and limbs, we decided to investigate the effect of prolonged local cooling on the healing of thermal burns in the rat.

* Carried out with the aid of a grant from the National Research Council of Canada under the direction of the Surgical Subcommittee on Shock.

METHODS

Except for preliminary experiments, male hooded rats from the same laboratory colony, five to six months of age, and weighing 300 to 350 Gm., were used. The tail of the rat was burned in the following experiments because among the common laboratory animals the skin of the rat's tail is covered with the least amount of hair. It was thought for this reason that among various experimental animals the reaction of the skin of a rat's tail to a burn might

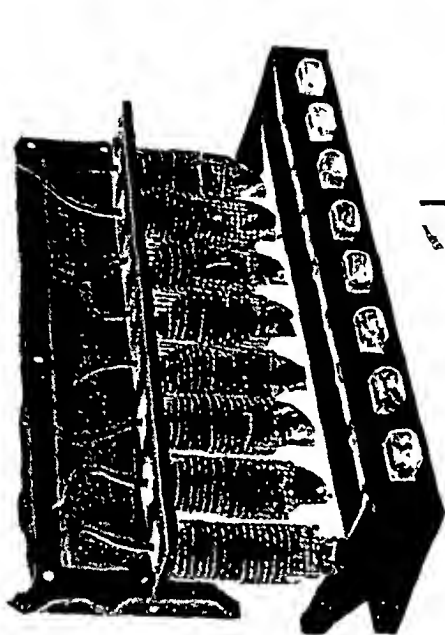


FIG. 1

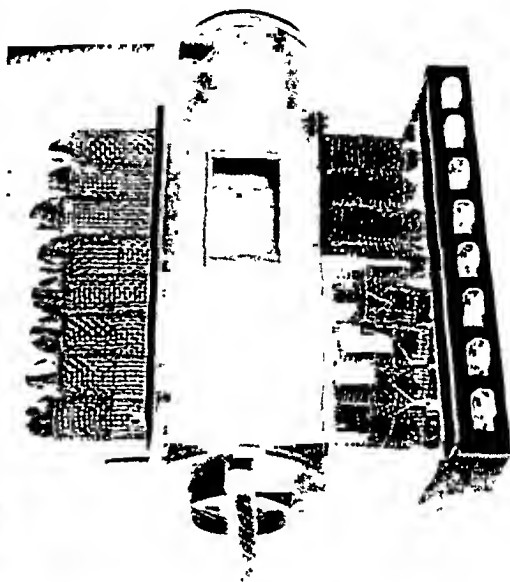


FIG. 2

FIG. 1.—Wire cages arranged to restrain the rats and to prevent them from chewing their tails. The food cups and water bottle rack can be seen. The tails pass through large holes in the board to which the cages are attached. Their tails rest on a gauze tray. This gauze rack is fixed so that the tails are not dependent.

FIG. 2.—Cages similarly arranged to those of Figure 1 but attached to the side of a cooling chamber. The tails pass through large holes in the sides of this chamber and rest on the gauze tray seen through the window.

most closely approximate the reaction of the human skin when it is burned. Preliminary experiments demonstrated that immersion of the rat's tail in water at 100°C. for three seconds consistently produced a moderate degree of tissue damage upon which a reduced temperature might be expected to create some observable effect either beneficial or harmful. For this reason in the following experiments in which a burn was produced the tails were burned for three seconds in water at 100°C. Only the terminals 13 cm. of each tail were burned. This was designated a "standard burn" and will be referred to subsequently as "S. B."

The rats to be burned were anesthetized in an ether chamber for two minutes in a uniform concentration of ether and the tail was then given a S. B.

HYPOTHERMIA IN BURNS

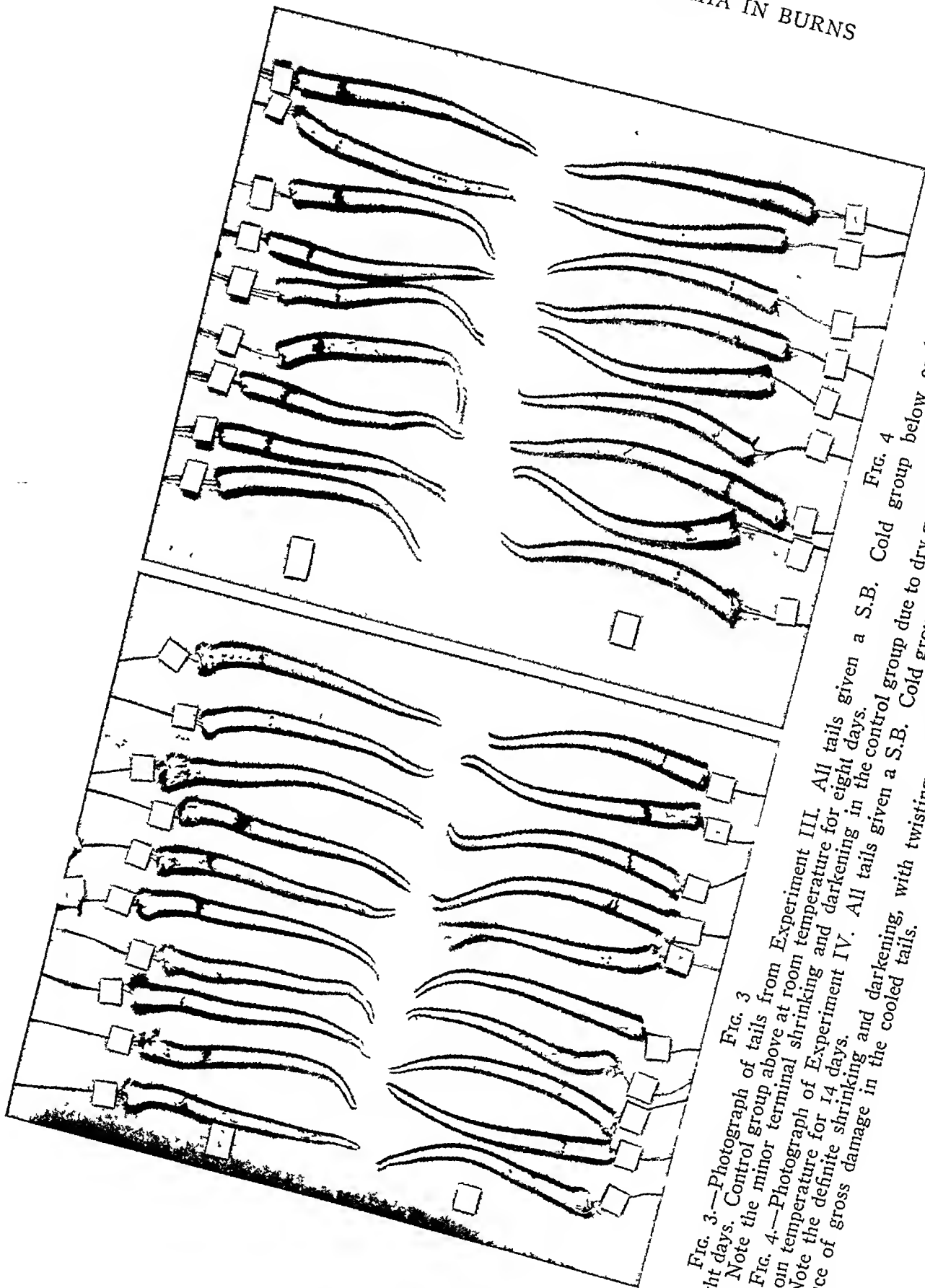


FIG. 3.—Photograph of tails from Experiment III. All tails given a S.B. Cold group below cooled at 52°F. for eight days. Control group above at room temperature for eight days. Note the minor terminal shrinking and darkening in the control group.

FIG. 4.—Photograph of Experiment IV. All tails given a S.B. Cold group below cooled at 44°F. for 14 days. Controls above at room temperature for 14 days. Note the definite shrinking and darkening, with twisting of the terminal portion of the control tails. There is very little evidence of gross damage in the cooled tails.

Following the experimental burn and before recovery from the anesthetic, the rats were placed in the cages shown in Figures 1 and 2. The tails of the rats were placed in an insulated metal cylinder (Fig. 2) through which circulated cold air. The temperature of this chamber could be regulated from 36°F. to room temperature and was controlled by a thermostat to within $\pm 2^\circ\text{F}$. The



FIG. 5.—Photograph of tails from Experiment V. All tails were given a S.B. The tails of the cold group were cooled at 40°F. for 11 days, then gradually brought up to room temperature during the next seven days, and kept at room temperature for ten days. Controls were kept at room temperature for 28 days.

Control tails above show a definite terminal dry gangrene. The cold tails below show a more extensive gangrene which is moist in type. This is associated with swelling and blebbing of all the burned area and, occasionally, slight swelling proximal to the burn.

cold air was prevented from leaking too freely from the chamber and unduly chilling the rats by means of a loose, rubber diaphragm through which the tail was inserted. The hole in the diaphragm was made large enough to accommodate the tail easily so that no mechanical interference with the circulation could occur from constriction. The control rats were placed in similar cages (Fig. 1) but their tails were exposed to room temperature varying from 75° to 80°F. After some experimentation it was found that tape collars attaching

the rats to the anterior part of the cage restrained them most efficiently and interfered least with their well-being and, therefore, prolonged the survival period. Access to as much purina fox chow and water as the rats desired was provided by means of the feeding and watering racks seen in Figures 1 and 2. The hind quarters and proximal part of the tails of the rats were kept clean by allowing the excreta to pass through large holes in the rear of the cages. The tails of all rats surviving for the duration of each experiment and the tails which seemed of interest from rats dying during the experiment were examined grossly and histologically. A daily chart of the appearance of each tail was kept and correlated with the histologic findings. The whole tails were fixed in 10 per cent formalin; blocks were decalcified, embedded in paraffin and sections stained with hematoxylin and eosin. Three transverse sections were taken from each of the tails, one at the proximal end of the burned area, one from the middle of the burned area and one from a point one inch proximal to the tip of the tail. Microscopically, the degree of damage was studied by estimating the amount of separation of the epidermis, the degree of edema, necrosis, hyperemia and cellular inflammatory reaction in the epidermis, dermis, subcutaneous tissue and muscle. The changes were graded as from one plus to four plus according to the amount of damage. Eight experiments in all were carried out and a total of 277 rats were used in these experiments.

EXPERIMENTS AND OBSERVATIONS

Experiment I.—Eight rats were placed in the control cages without burning the tails and kept for 29 days (Fig. 8).

At the end of 29 days the tails of the four survivors appeared normal on gross and microscopic examination.

Experiment II.—Sixteen rats were used in this experiment and none of the tails were burned. The apparently normal tails of these 16 rats were placed in the cooling chamber at 52°F. The tails of eight rats were cooled for seven days and then removed to room temperature. The tails of the remaining eight rats were cooled at 52°F. for a total period of 14 days and then changed to room temperature. At the end of 24 days from the beginning of the experiment all the survivors were killed.

Four animals from each group survived for the duration of the experiment. One tail from the group that was cooled for 14 days presented edema throughout the whole length of the tail which appeared to be due to kinking of the tail early in the experiment. The tails of the seven remaining survivors could not be distinguished in the gross from normal tails. However, microscopic examination revealed a definite though slight shrinking and irregularity of the nuclei of the epidermis, sweat glands and hair follicles. These changes were associated with a minimal loss of the definite outline of the collagen bundles of the dermis. Of more interest was the relaxed and dilated appearance of small and large arteries and veins, associated with a dense packing and clumping of red blood cells within them.

Experiment III.—The tails of 32 rats were given a S.B. The 16 tails of the experimental group were kept at 52°F. for eight days and the 16 tails of the control group were kept at the room temperature for the same period.

Thirteen of the control rats and ten of the experimental rats survived for eight days. A comparison of the appearance of the tails of these rats at the termination of the experiment can be seen in Figure 3. Those of the control group showed a definite dry gangrene of the terminal part of the tails extending for a distance of from one to three centimeters. In the cooled group only a few tails showed minor gross changes at the

tip, while the remainder of the group showed no gross evidence of damage. It was interesting to note during the experiment that the tips of the control tails showed some cyanosis about the 2nd or 3rd day. This condition spread proximally as the distal part became gangrenous. All of the control rats showed a slight swelling of the whole tail for about the first three days, which gradually disappeared as the experiment proceeded.

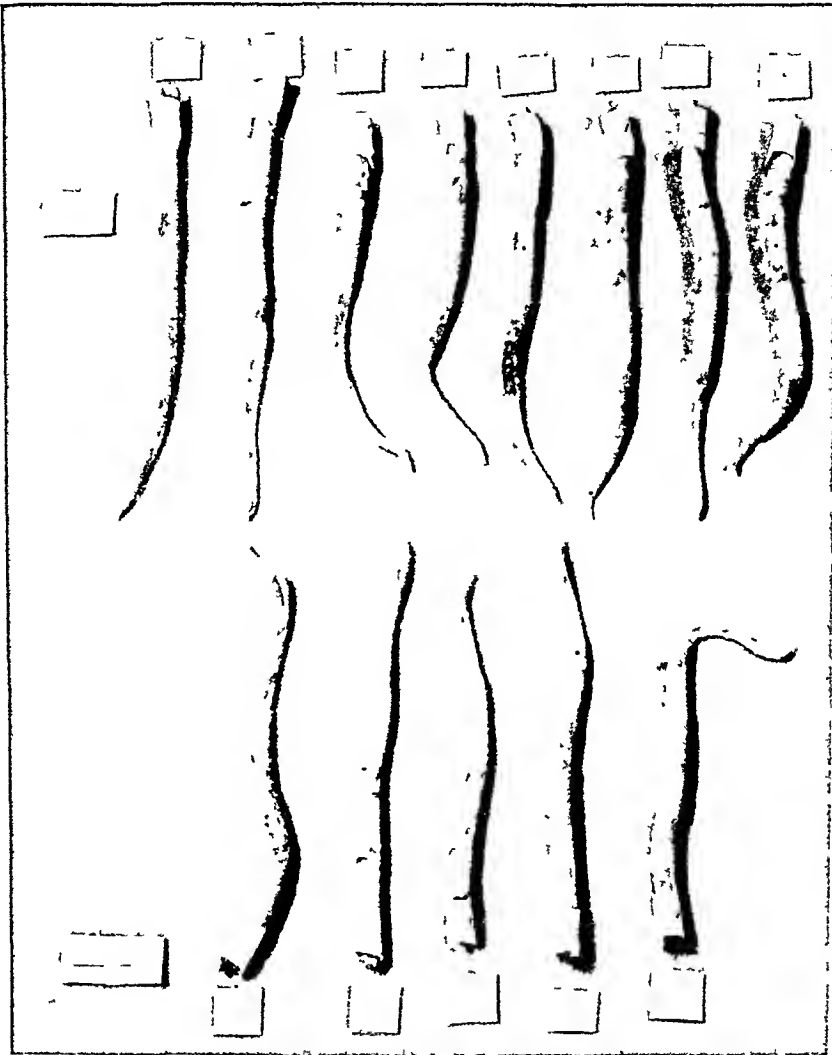


FIG. 6.—Photograph of tails from Experiment VI. All tails were given an S.B. The cooled tails were placed in a temperature of 54°F. for four days, then raised to room temperature during the next six days, and kept at that temperature for eight days. Control tails were kept in room temperature for 18 days.

The control tails below show a definite dry gangrene of the terminal segment. There is more extensive moist gangrene in the experimental group above, associated with swelling and blebbing of all the burned area.

In the experimental group this early swelling never appeared. Many of the experimental tails showed slight cyanosis of the tip about the 3rd day, which then gradually disappeared leaving the tail a normal white color and of soft consistency. The rats with their tails in the cold chamber showed less evidence of painful stimuli following the burns than did the control rats.

HYPOTHERMIA IN BURNS

The microscopic changes corresponded fairly closely with the gross appearance although the gross changes in the terminal part of the controls were more obvious than the microscopic. Conversely, the microscopic changes in the proximal portion of the tails in both groups were more evident than the gross changes. The terminal part of the control tails presented necrosis of all tissues. In the proximal portions of the tails it is interesting to note that hyperemia was more marked in the cooled tails than in the

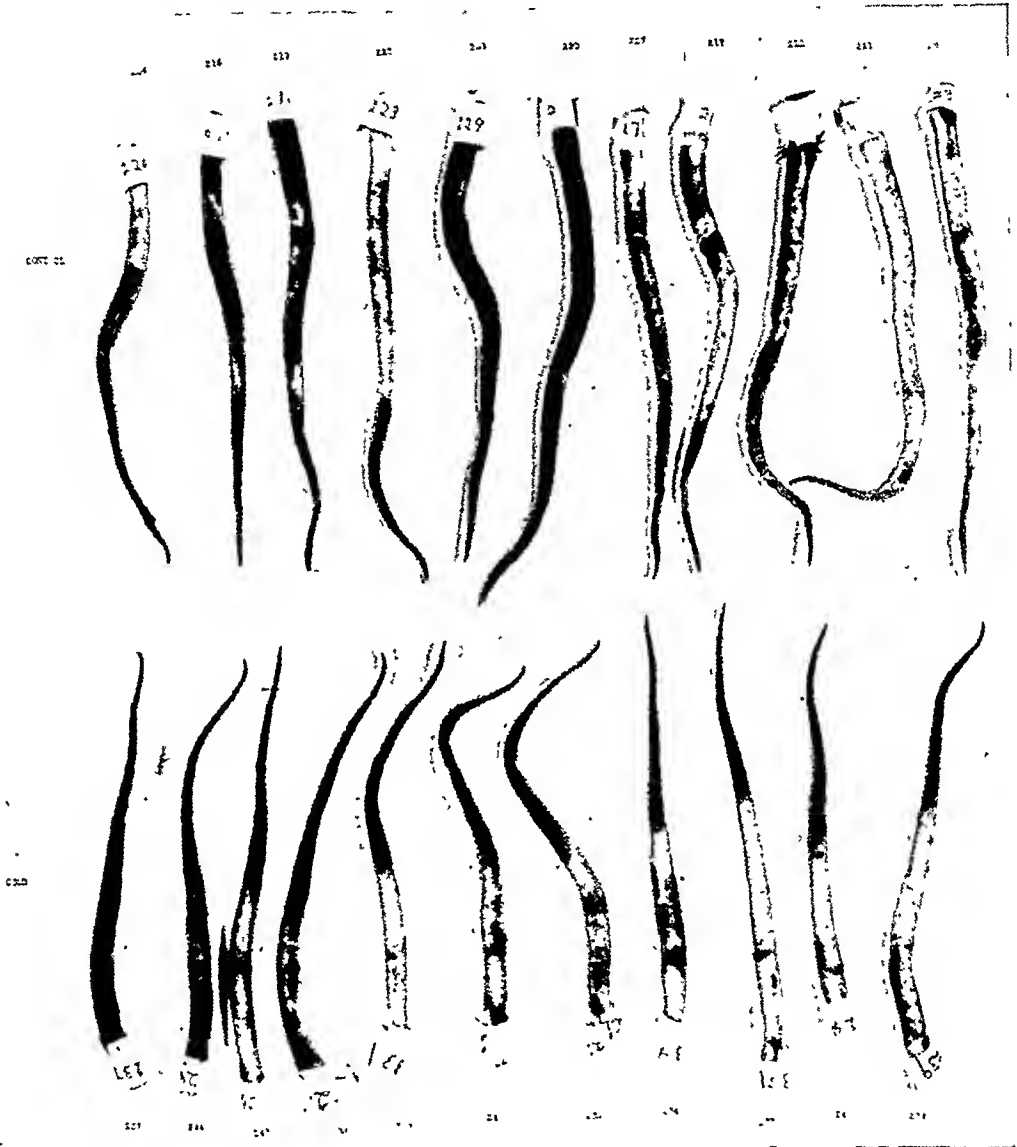


FIG. 7.—Photograph of Experiment VIII. All tails given a S.B. Cooled tails below were kept in a temperature of 63°F. for six days, and then gradually brought up to room temperature during the next five days, and kept in this temperature for 13 days. Control tails above were kept in a temperature of 85°F. for 24 days.

There is a slightly more extensive dry gangrene of the terminal part of the tail than is seen in the control tails.

controls. In the terminal portions of the treated tails the large arteries and veins were dilated, their walls stretched and relaxed, and their lumina often presented marked silting of the red blood cells which appeared to plug the vessels. In the experimental animals the epithelium seemed thicker and less dried out in appearance than that of the controls (Figs. 9 and 10).

Experiment IV.—The tails of 32 rats were given a S.B. The tails of the experimental group were kept at a temperature of approximately 44°F for 14 days. The controls were kept at room temperature.

Nine of the control rats and nine of the treated rats survived for 14 days. The appearance of the tails of these rats at the termination of the experiment is seen in Figure 4. The nine control tails showed changes of a similar nature to those of Experiment III but they were more extensive. The dry gangrene was pronounced and was present in the terminal 2 to 5.5 centimeters. Proximal to this was a cyanotic area and then a band of hyperemia. Two tails of the cooled group presented dry gangrene of the distal centimeter and two other tails showed cyanosis of the distal 4 centimeters but these tails were soft. The remaining five tails of this treated group which survived were white and soft. The time of appearance of the changes in Experiment IV were similar to those of Experiment III. Again the controls showed a generalized swelling of the tails during the first three days following the burn which then disappeared. The cooled tails did not show this early swelling.

The microscopic findings of the 18 survivors paralleled the gross changes. The tails from both groups presented a washed-out appearance in all the soft tissues of the distal half of the tail. In the cooled group nuclear staining was very faint. The epidermis was thicker than in the control group. Again, the most significant microscopic finding in the tails of the treated group was the hyperemia and the silting of red blood cells found in blood vessels of all sizes in many of the tails.

Experiment V.—The tails of 32 rats were given a S.B. The tails of the experimental group were cooled for the first 11 days following the burn in temperatures of 40°F., and then during the next seven days the temperature was gradually brought up to room temperature. The tails were then kept in this temperature for a further ten days, making a total of 28 days for the experiment. The controls were kept at room temperature for the same length of time.

Six of the control rats and four of the treated rats survived for 28 days. The tails of these rats are seen in Figure 5. The tails of the control group showed a dry gangrene of the distal 2.5 to 8 centimeters. One tail was edematous and hyperemic above the dry gangrene to the upper level of the burn. The tails of the four treated surviving rats showed *more* damage than the controls. At the termination of the experiment all of these cooled tails were tremendously swollen from the tip to a centimeter or two above the proximal level of the burn. They were hyperemic and extensive maceration of the skin was present throughout the whole edematous area. It is interesting that all of these tails appeared quite normal for the 11 days that they were maintained at the temperature of 40°F., and the seven days during which the temperature was gradually raised to the room temperature. Furthermore, no gross pathologic changes were noted until approximately four days after the temperature had been maintained at this level. During the following seven days with the treated tails at room temperature, severe damage progressed rapidly with the development of extensive moist gangrene. At the termination of the experiment the moist gangrene of the treated tails produced more damage than was present in the control tails.

Microscopically, nuclei were absent from the skin and subcutaneous tissue of the gangrenous areas of the control tails while in the treated tails nuclear staining was gone throughout the length of the burned area. Polymorphonuclear leukocytes were present in the skin and subcutaneous tissue of the control tails and absent in the treated tails while edema and hyperemia were more prominent in the proximal segments of the treated tails than in the controls.

Experiment VI.—Thirty-two rats were given a S.B. The tails of the cooled group were kept at 54°F. for four days, and then during the next six days the temperature was gradually brought up to room temperature and held for eight days. The total duration of the experiment was 18 days. The control tails were maintained at room temperature for the same period of time.

Five of the control rats and ten of the treated rats survived 18 days. These tails are seen in Figure 6. The tails of the control group showed a dry gangrene of the terminal 5 to 6.5 centimeters while the tails of the treated survivor group showed a moist gangrene

of the terminal 5 to 9 centimeters with occasional blebs proximal to the gangrenous area. Except for a slight terminal cyanosis, all of these tails appeared relatively normal for the four days that the temperature was maintained at 54°F. On the 6th and 7th days this temperature was gradually brought up to 70°F. On the 7th day most of the tails began to show a definite gangrene of the tip which progressed rapidly to an extensive moist gangrene by the 18th day when all of the rats were killed.



FIG. 8



FIG. 9

FIG. 8.—Photomicrograph of normal tail. (Hematoxylin and eosin stain, $\times 51$). Note the moderate thickness of the wall of the caudal artery and the definite outline of muscle fibers in the wall.

FIG. 9.—Photomicrograph of control tail from Experiment III. (Hematoxylin and eosin stain, $\times 48$). Tail given a S.B. and kept at room temperature for eight days. Note the contracted caudal artery in contrast to the experimental tail of Figure 10, from the same experiment.

Microscopically, the necrosis of skin and subcutaneous tissue was slightly more prominent in the controls than the treated tails and there was a good deal of polymorphonuclear infiltration of the skin and subcutaneous tissues of the control tails. Two things of particular interest were present in sections of the treated tails. First, the sections of the terminal part showed a marked dilatation of the large veins which were filled with a brownish homogeneous material composed of laked red blood cells; and, secondly, the large arteries of the more proximal part of the tail were markedly dilated until there was no wrinkling of the internal elastic lamina. Other medium-sized to small veins were dilated and filled with blood. The large arteries of the control tails were extremely contracted.

Experiment VII.—The tails of 24 rats were given a S.B. Of these, eight were cooled at 63°F. for 36 hours. At the end of this period the rats were placed in room temperature. The tails of the 16 control rats were kept at room temperature. The experiment was continued for 18 days at which time the survivors were killed.

Nine of the control animals and four of the group cooled for 36 hours survived until the end of the experiment. It was interesting to observe that the cooled tails developed cyanosis and gangrene very gradually after being removed to room temperature, and were in this temperature usually seven to ten days before very marked changes occurred. However, at the end of the experiment the survivors from the experimental group presented a degree of dry gangrene equal to the control group.

Microscopic examination of sections of the tails of the survivors revealed little difference in the degree of necrosis between the cooled tails and the controls. However, eight hours after scalding the tails of the rats in this experiment, one control and one experimental rat were killed and the effect of eight hours cooling was studied microscopically. Sections of the cooled tail revealed dilatation of blood vessels and silting of red blood cells that was not observed in the control killed at the same time (Figs. 12 and 13).

Experiment VIII.—The tails of 32 rats were given a S.B. Sixteen of the tails were cooled at 63°F. for six days, and then during the next five days the temperature was gradually raised to room temperature and this was maintained for another 13 days. The tails of the remaining 16 rats used as controls were warmed to a temperature of 85°F., in contrast to the usual room temperature of 75°F. to 80°F. used for all previous control animals. All survivors were killed on the 24th day of the experiment.

Thirteen of the experimental and 12 of the control animals survived for the duration of the experiment. It was interesting to note that the cooled tails developed some cyanosis of the tip of the tail within 24 to 48 hours of the burning and that this cyanosis persisted and increased. Moreover, within nine days of the burn, while still in the cool box they showed a dry gangrene of the tip. As the temperature was gradually raised to the room temperature, the dry gangrene spread more rapidly. There was a marked increase in the rate of extension of the gangrene about the 3rd day after the cooled tails had been exposed to room temperature. At the termination of the experiment the gangrene was more extensive in the cooled tails than in the control tails (Fig. 7). The tails of the group kept at 85°F. showed a more rapid development of gangrene than in the previous controls kept at room temperature. There were also more blebs proximal to the gangrene than were seen in previous controls.

Microscopic examination of the cooled and uncooled tails revealed only minor difference in the degree of necrosis but there was more edema, vascular dilatation and clumping of red blood cells in the cooled tails.

FIG. 10.—Photomicrograph of experimental tail from Experiment III. (Hematoxylin and eosin, x 83).

Tail given a S.B. and then cooled at 52°F. for eight days. Note the dilated caudal artery and dense packing of red blood cells in the lumina of artery and vein.

FIG. 11.—Photomicrograph from Experiment II. (Hematoxylin and eosin, x 51). Tails not burned, cooled 14 days at 52°F., and then at room temperature for ten days.

Note the dilated caudal artery with thinned-out wall and lumen packed with red blood cells.

FIG. 12.—Photomicrograph of control tail from Experiment VII. (Hematoxylin and eosin stain, x 54).

Tails given a S.B. and kept in room temperature for eight hours. Note the thick muscular wall of the caudal artery.

FIG. 13.—Photomicrograph of cooled tail from Experiment VII. (Hematoxylin and eosin stain, x 51).

Tail given a S.B. and cooled at 63°F. for eight hours and killed immediately on removal from refrigeration chamber.

Note the dilated caudal artery with thinned-out muscle in contrast to that of Figure 12. The lumen is packed with red blood cells.

FIG. 10



FIG. 11



FIG. 12



FIG. 13

DISCUSSION.—Many reports have appeared in the literature regarding the beneficial effect of cooling damaged tissues.^{15, 16, 17} In view of the relatively superficial nature of the injury in burns it might be anticipated that hypothermia would provide an ideal method of reducing tissue damage and of promoting healing. The results of our experiments on the effect of hypothermia on scald burns of rats' tails indicates that this type of therapy is definitely harmful to the burns under the experimental conditions previously described. Preliminary experiments (Nos. I and II) showed, respectively, that neither the position of the tails in the refrigeration chamber nor the cooling of the *normal* tails, caused any obvious gross pathologic changes although microscopic sections of the cooled tails presented a slight dilatation of blood vessels and hyperemia. While this was not very obvious its appearance suggested some disturbance of circulation due to the cooling. However, an apparently beneficial effect of cooling burned tails was noted grossly when the animals were sacrificed immediately after the period of cooling (Experiments III and IV). In spite of this grossly normal appearance, the microscopic findings of dilatation of blood vessels and the silting of red blood cells indicated that the cooling had affected the circulation of the tails in some way. That the cooling had caused serious damage became apparent when burned tails which had been cooled at a fairly low temperature were allowed to survive for some time at room temperature (Experiment V). Thus, the microscopic changes noted in Experiments III and IV were given time to develop into grossly observable damage. The only constant microscopic change which appeared to be due to the cooling of the tails *per se* was the dilatation of blood vessels and the silting of red blood cells seen in these vessels. Varying degrees of these changes were noted in all tails that were cooled. They were noted in unburned tails cooled at low temperatures for long periods of time, and were also seen in tails cooled at 63°F. for only eight hours. Similar changes were present in the burned tails cooled at identical temperatures and for the same length of time. These alterations persisted for as long as two weeks after the tails were removed to room temperature. These constant findings suggest that they were related to the severe damage noted in the later experiments. In these latter experiments on cooling burned rats' tails the reduced temperatures ranged from 40°F. to 63°F. and were maintained for varying periods of time—from eight hours to two weeks. In all these experiments in which the rats survived for some weeks at room temperature after the period of cooling the treated tails were more severely damaged than the controls. Visible evidence of the damage became marked within a few days after the temperature was elevated and constantly appeared whether it was raised suddenly or gradually to room temperature. In one experiment (No. VIII) the control tails were maintained at a temperature of 85°F., which was approximately 10°F. above the room temperature used for the controls of other experiments. In the controls of this group gangrene developed more rapidly than in the control tails of other experiments. It is interesting to note that the least degree of damage of all the burned tails studied in these experiments was found in the control tails main-

tained at 75°–80°F. and in the cooled tails of Experiment No. VII. In this latter experiment the tails were cooled for 36 hours at 63°F.

These results are contrary to those of other investigators, who have claimed beneficial results in the therapy of burns with cold.^{18, 6, 19, 20} Several authors^{15, 16, 17} have shown that ischemic tissues can be preserved much longer by early refrigeration than at room temperatures and the evidence on this point is convincing. Allen,¹⁸ Allen, *et al.*,⁶ Crossman,¹⁹ and Pickerill,²⁰ reasoning partly by analogy, have advocated the use of rather low temperatures in the treatment of burns. Although the use of cold may be satisfactory in preserving recently ischemic tissues there seems to be insufficient evidence that it is beneficial in the healing of fresh burns. The clinical evidence supporting the claims of all these authors, so far as we are aware, is based on the impression of only three reported cases.

In view of the fact that our experimental results conflict with the clinical reports of Allen,¹⁸ and others,^{6, 19, 20} it is important to investigate the factors which could explain the adverse effects of cold noted in our present study. Recently, there has been a renewed interest in the effect of reduced temperatures on tissues and much experimental evidence has been accumulated that may throw some light on the cause of the damage noted in the rats treated by hypothermia in this present study.

The first important clue to the cause of the harmful effects of cooling burned rats' tails in our experiments was the relaxation and dilatation of the blood vessels associated with the plugging of many of the lumina with red blood cells observed in *burned* and *unburned* tails which had been cooled (Figs. 10, 11 and 13). Greene²¹ observed that clumping of red cells and obstruction of dilated vessels were features of the initial reaction to low, dry cold. Ricker²² decided that this stasis which accompanied chilling of tissue resulted from a vasoparalysis while Tannenberg²³ believed that the mechanism was due to the exudation of serum leaving the vessels packed with red blood cells. Jochim and Hertzman²⁴ believe that engorgement and damage of the capillary tree occurs because of arteriolar dilatation occurring before the arteriovenous anastomoses open. Grant²⁵ has shown how these anastomoses respond to local thermic stimuli. All of these authors agree that the final outcome of these phenomena is a plugging of the circulation and consequent anoxia of the tissues.

The next finding of importance was the development of edema leading to extensive moist gangrene in the burned tails which were returned either gradually or suddenly to room temperature after cooling (Figs. 6 and 7). That this edema was not a result of constriction of the tails was proved by Experiment I, where rats with unburned tails were left in the experimental cages for one month without harmful effects. This development of edema is in agreement with Smith, Richie and Dawson,²⁶ who found that hemorrhage in addition to exudation took place especially after the warming of chilled tissues. Others have noted edema during prolonged cooling^{12, 27} which often remained after the temperature had returned to normal.²⁷ This edema might be due to capillary damage secondary to the vascular dilatation of vessels and plugging

with red blood cells noted by ourselves and others. However, Lewis²⁸ also believed that cooling of tissues by temperatures of the order used in these experiments and applied for as short a time as two hours, damages the tissues, possibly liberating histamine-like substances which produce hyperemia and edema. Safford and Nathanson²⁹ suggest that the damage which occurs following a sharp rise in temperature of previously cooled tissue is, in reality, a burn and this results in edema. More recently, degeneration of peripheral nerves has been noted in chilled tissues.^{30, 31} Large and Heinbecker³⁰ suggest that this results in damage to tissues by a loss of normal trophic impulses. It is quite conceivable that this latter observation may be the basis for altered circulation and consequent edema.

Before attempting to draw any general conclusion from these experiments regarding the effect of cooling thermal burns there are a few points that should be mentioned regarding the structure of the tail of the rat which may have operated in producing the results in these experiments, and which might not be operative in other areas of the body. For instance, it is apparent from the controls of our experiments that the scald burns caused sufficient damage to produce a gangrene of all tissues of the distal 6 to 7 centimeters of the tail. For this reason it seems likely that the tail of the rat is sufficiently small that the scald burn used may have penetrated the entire thickness of the distal part of the tail, producing an irreparable degree of damage. It is worth noting, however, that in spite of this irreparable damage the initial cooling did prevent the changes characteristic of necrosis, and these findings agree with Large and Heinbecker who found that the normal response to injury did not appear about incisions made in cooled limbs of dogs. On removal to room temperature severe damage appeared in the burned tails and this observation parallels Large and Heinbecker's finding that their incisions showed an exaggerated response when the cooling was stopped.¹² It is possible that the severe damage which appeared in the cooled tails after elevating the environmental temperature was due to the fact that the skin of the rat's tail provides a thick, unyielding envelope about the tissues, which would increase the obstruction to blood flow resulting from any edema of the enclosed tissues. For this reason it is possible that any harmful effects which the refrigeration may have produced in the tissues and which appeared when the tails were removed to a temperature of 75°F. was exaggerated beyond that which might occur in the cooling of broad surfaces covered with a more delicate skin.

In conclusion, it may be said that the observations in the preceding experiments of this paper indicate that prolonged cooling of only moderate degree induces vasodilatation which is present while the tissues are being cooled and which persist for a long time when the same tissues are again placed in a normal environmental temperature. Greene²¹ working with mice at temperatures which produce true frost bite, Lewis²⁸ working with humans and using temperatures as high as 59°F., and, recently, Friedman³² in an extensive study of trench foot have all stated that one of the early responses to cold is a vasodilatation. According to Lewis²⁸ this response is a physiologic defense mechanism

within certain limits. In many of the observations of these workers, the vasodilatation was noted when the tissues were reëxposed to normal temperatures for some time. Our results confirm the views of these investigators and indicate that a permanent vasoparalysis occurs while tissues are being cooled at temperatures as high as 63°F. for a period of eight hours. These results, and the vasodilatation of trench foot³² and chilblain²⁸ which occurs in temperatures above that of freezing, make it abundantly clear that a breakdown of the neurocirculatory system can occur in tissues which are cooled, but not frozen.

It is not possible to say whether or not this disturbance of vasomotor control due to cooling was responsible for the poor healing of the burns in the preceding experiments. However, it can be concluded from these results that external temperatures ranging from 40°F. to 63°F. are harmful when applied to a scald burn of the rat's tail. Moreover, it was noted that the lowest temperature resulted in the most severe damage, while a temperature of 63° F. for a relatively short period produced only slightly more damage in the burned tails than occurred in the burned control tails in room temperature of 75°F. Because of the severe burn produced in these experiments and because of the nature of the rat's tail, it would seem unjustifiable to infer that similar treatment of thermal burns in the human would produce analogous results. In view of this, it is interesting to observe that while most of the controls were kept at an environmental temperature of 76°F. the control tails of Experiment No. VIII were kept in a temperature of 85°F. and these latter tails showed more severe damage than the controls kept at 76°F. This finding suggests that the optimum temperature for the treatment of the burns in these experiments was between 65° and 75°F. This coincides with the temperature that Elman, *et al.*¹⁰ found to be associated with the lowest mortality from burn shock in rats and, moreover, these temperatures are relatively cool as compared to the usual temperature to which patients suffering from burns are exposed. These temperatures for the treatment of burns agree with those of Rossiter,³³ and Safford and Nathanson²⁹ who have recommended the use of temperatures of the order of 70°F. for treatment of burns.

For these reasons it would seem of value to extend these experiments to the human. However, it would be wise in such experiments to commence with temperatures of about 70°F. and proceed with caution as lower temperatures are used, especially when applied to small extremities. Safford and Nathanson²⁹ reported the treatment of a lesion, possibly a burn, by refrigeration and noted that when the temperature was raised, retrogressive changes occurred until the 89th day of refrigeration. This indicates that refrigeration must be done not only at moderate temperatures but also over a long period of time, and great care must be taken not to raise the temperature too soon nor too suddenly. Moreover, in such treatment of extensive burns, great care should be taken to prevent lowering the general body temperature below normal.

We wish to thank the Coca Cola Co. of Canada, and the Electrolux Co. of Canada, for the loan of equipment necessary for the construction of the refrigeration chamber used in this study.

BIBLIOGRAPHY

- ¹ Fay, T.: Observations on Prolonged Human Refrigeration. New York State J. Med., 40, 1351-1354, 1940.
- ² Allen, F. M.: Reduced Temperatures in Surgery: Surgery of Limbs. Am. J. Surg., 52, 225-237, 1941.
- ³ Allen, F. M.: Reduced Temperatures in Surgery: Experiments on Pelvic and Abdominal Refrigeration, with Especial Reference to Traumatic and Military Surgery. Am. J. Surg., 55, 451-466, 1942.
- ⁴ Crossman, L. W., and Allen, F. M.: Principles of Surgical and Therapeutic Refrigeration. Surgical Clinics of North America. April, 1945, New York Number.
- ⁵ Webster, D. R., Woolhouse, F. M., Johnston, J. L.: Immersion Foot. J. Bone and Joint Surg., 24, 785-794, 1942.
- ⁶ Allen, F. M., Crossman, L. W., and Safford, F. K. Jr.: Reduced Temperature Treatment for Burns and Frostbite. New York State J. Med., 43, 951-952, 1943.
- ⁷ Fay, T.: Cooling in Shock. J. A. M. A., 121, 1109, 1943.
- ⁸ Blalock, A.: Comparison of Effects of Local Application of Heat and of Cold in Prevention and Treatment of Experimental Traumatic Shock. Surgery, 11, 356-359, 1942.
- ⁹ Sellers, E. A., and Willard, J. W.: The Effect of Plaster Bandages and Local Cooling on Hemoconcentration and Mortality Rate in Burns. Canad. M. A. J., 49, 461-464, 1943.
- ¹⁰ Elman, R., Cox, W. M. Jr., Lischer, C. E., and Mueller, A. J.: Mortality in Severe Experimental Burns as Affected by Environmental Temperature. Proc. Soc. Exper. Biol. and Med., 51, 350-351, 1942.
- ¹¹ Rose, H. W.: Initial Cold Water Treatment for Burns. Northwest. Med., 35, 267-270, 1936.
- ¹² Large, A., and Heinbecker, P.: Effect of Cooling on Wound Healing. ANNALS OF SURGERY, 120, 727-741, 1944.
- ¹⁴ Sano, M. E., and Smith, L. W.: Effect of Lowered Temperatures upon the Growth of the Fibroblasts *in vitro*: Its Application to Wound Healing. J. Lab. and Clin. Med., 27, 460-464, 1942.
- ¹⁴ Nemoto, M.: Influence of the Temperature upon the Life Duration and the Growth of the Fibroblast Cultured *in vitro*. Tohoku J. Exp. Med., 41, 70-78, 1942.
- ¹⁵ Allen, F. M.: Resistance of Peripheral Tissues to Asphyxia at Various Temperatures. Surg., Gynec. and Obst., 67, 746-751, 1938.
- ¹⁶ Brooks, B., and Duncan, G. W.: Effects of Temperature on the Survival of Anemic Tissue: Experimental Study. ANNALS OF SURGERY, 112, 130-137, 1940.
- ¹⁷ Freeman, N. E.: Influence of Temperature on Development of Gangrene in Peripheral Vascular Disease. Arch. Surg., 40, 326-333, 1940.
- ¹⁸ Allen, F. M.: Theoretical and Experimental Aspects of Surgical Refrigeration. Canad. M. A. J., 51, 220-226, 1944.
- ¹⁹ Crossman, L. W.: Refrigeration for the Preservation of Traumatized Tissues. Canad. Hosp. J., 21, 30-32, August, 1944.
- ²⁰ Pickerill, H. P.: Reorientation in Treatment of Burns. New Zealand M. J., 41, 70-78, 1942.
- ²¹ Greene, R.: Immediate Vascular Changes in True Frostbite. J. Path. and Bact., 55, 259-267, 1943.
- ²² Ricker, G.: Pathologie als Naturwissenschaft; Relationspathologie für Pathologen, Physiologen, Mediziner und Biologen. Julius Springer, Berlin, 1924.
- ²³ Tannenbunrg, J.: and Fischer-Wasels, B.: Handbuch der norm. und path. Physiol., 7, 1496, 1927.
- ²⁴ Jochim, K. E., and Hertzman, A. B.: The Effects of Cold on the Blood Vessels of the Skin of the Forearm. Proc. Fed. Am. Soc. Exper. Biol., 3, 22, 1944.
- ²⁵ Grant, R. T.: Observations on Direct Communications between Arteries and Veins in Rabbit's Ear. Heart, 15, 281-303, 1930.

- ²⁶ Smith, J. L., Richie, J., and Dawson, J.: On the Pathology of Trench Frostbite. *Lancet*, 2, 595-598, 1915.
- ²⁷ Ungley, C. C., and Blackwood, W.: Peripheral Vasoneuropathy after Chilling: Immersion Foot and Immersion Hand, with Note on Morbid Anatomy. *Lancet*, 2, 447-451, 1942.
- ²⁸ Lewis, T.: Observations on some Normal and Injurious Effects of Cold upon Skin and Underlying Tissues; (a) Reactions to Cold, and Injury of Normal Skin. *Brit. M. J.*, 2, 795-797, 1941. (b) Chilblains and Allied Conditions. *Brit. M. J.*, 2, 837-839, 1941.
- ²⁹ Safford, F. K., Jr., and Nathanson, M. B.: Clinical Observations on Tissue Temperatures: Pathologic and Therapeutic Effects. *Arch. Surg.*, 49, 12-22, 1944.
- ³⁰ Large, A., and Heinbecker, P.: Nerve Degeneration following Prolonged Cooling of Extremity. *ANNALS OF SURGERY*, 120, 742-749, 1944.
- ³¹ Blackwood, W., and Russell, H.: Experiments in Study of Immersion Foot. *Edinburgh M. J.*, 50, 385-398, 1943.
- ³² Friedman, N. B.: The Pathology of Trench Foot. *Am. J. Path.*, 21, 381-434, 1945.
- ³³ Rossiter, R. J.: Plasma Loss in Burns. *Bulletin of War Medicine*. 4, 181-189, 1943.

STREPTOMYCIN IN SURGICAL INFECTIONS:

I—LABORATORY STUDIES*

MAJOR EDWIN J. PULASKI, M.C., A.U.S.†

AND

MAJOR HELMUTH SPRINZ, M.C., A.U.S.

WITH THE TECHNICAL ASSISTANCE OF

CARROLL E. HEIST, B.S., AND HELEN B. EHRHORN, B.S.

STATEN ISLAND, N. Y.

FROM THE HALLORAN GENERAL HOSPITAL, STATEN ISLAND, N. Y.

It is now well established that successful clinical results from antibiotic therapy depend on accurate bacteriologic diagnosis and proven susceptibility *in vitro* of the causal organisms to the chemotherapeutic agent. Research on the clinical effectiveness of streptomycin in certain types of infection afforded the opportunity of making extensive correlative laboratory studies. This communication reports some of the observations and results, including: (1) a broth serial dilution method for testing susceptibility of bacteria to streptomycin; (2) an adaptation of the method for assay of streptomycin in blood and urine; (3) data on absorption, excretion and distribution of the drug in the body; (4) results of susceptibility tests on 1,000 pure cultures of bacteria; (5) comparison of *in vitro* action of streptomycin and penicillin on the gram-positive cocci; (6) a dosage scheme evolved on the basis of the results of bacterial sensitivity tests and drug levels in body fluids; and (7) experiences with drug-fastness and its clinical implications.

1. *Broth Serial Dilution Test.*—The method, briefly, consists in determining the lowest concentration of streptomycin which will produce complete inhibition of growth of the organism to be tested. Wassermann tubes, each containing 2 cc. of a streptomycin standard solution in sterile distilled water, are seeded with 2 cc. of a six-hour broth culture of the organism, diluted 1:50 with broth. The broth employed has the formula, 2 per cent peptone, 1 per cent beef extract, 0.5 per cent sodium chloride, in water, adjusted to pH 7.8.

For routine clinical use we recommend a four-tube set-up, containing aqueous streptomycin standard solutions, of 8, 32, and 256 mcgm./cc.,‡ respectively, and a "water control" in the fourth tube. The addition of the bacterial suspension halves the concentration of streptomycin in the tubes. As a control on each set of determinations, a duplicate test is made, using a *Staphylococcus aureus* "SM" of known susceptibility. After 16 to 18 hours of

* This project was carried out as a part of the study being made under the direction of the Army Medical Research and Development Board, Office of the Surgeon-General.

† Present address: Brooke Army Medical Center, San Antonio, Texas.

‡ 1 mcgm. = 1 "S" unit.

incubation the inhibition is determined by noting the tubes in which no growth has occurred.

2. *Adaptation of Sensitivity Test to Assay of Blood and Urine.*—The sensitivity test has been adapted to the assay of streptomycin in blood and urine. Two cubic centimeters of blood serum is serially diluted with water in the range of 1:1 to 1:32. The same range of dilution is employed for urine, which has been previously diluted with 20 parts of distilled water because of the high concentration of streptomycin usually found in urine. Two-cubic-centimeter amounts of a 1:50 dilution of a six-hour culture of the test organism

TABLE I
BLOOD SERUM AND URINE STREPTOMYCIN LEVELS IN PATIENTS
RECEIVING 0.4 GM. DOSES I.M. EVERY 4 HOURS

Case No.	Blood Serum Assay	Urine Assay
15	4-16 Mcgm./cc.	400-1,200 Mlgm./cc.
16	8-16	800-1,200
17	8-16	800-1,200
27†	16-16	2,000+
28*	16-32	64- 256
29*	32-32	128- 256
40†	16-16	2,000-2,000+
42†	8-16	500-2,000
45†	8-32	500-4,000
53†	8- 8	500-2,000
54†	8-16	500-2,000+
59†	4-16	500-2,000

* Marked impairment of renal function.

† Fluid intake restricted to 2,000 cc./24 hrs.

in broth are added to the tubes containing 2 cc. of the serially-diluted body fluid being assayed. Results are read after 16 to 18 hours incubation. Since the growth of the *Staphylococcus aureus* "SM" is influenced by blood sera, we prefer a *K. pneumoniae* strain as the test organism. This bacterium grows luxuriantly in body fluids and gives a sharp end-point.

In assaying the blood and urine for streptomycin, it is important to set-up controls, using patient's blood serum and urine, obtained before the drug is administered. For this purpose 12 cc. of the patient's blood is drawn aseptically and the serum is separated from the clot by centrifugation. Pretreatment urine is collected and Seitz-filtered to render it sterile. Both are refrigerated until needed. Controls are necessary because of variation from day to day in the sensitivity of the test organism in body fluids. Two-tenths cubic centimeter of a 320 mcgm./cc. aqueous solution of streptomycin is mixed with 1.8 cc. of the body fluid in the first of six Wassermann tubes. The contents of this tube are serially diluted with water in the same manner as the test fluid. The concentration of streptomycin in the body fluid tested is then determined by comparing the end-point with that of the control. This assay method is similar to the technics of Donovan, *et al.*,¹ and Price, *et al.*²

3. *Absorption, Excretion and Distribution.*—Our data on the absorption and excretion of streptomycin are in substantial agreement with the findings of other workers.^{3,4,5,6,7} After intramuscular injection, which is the route of

choice, effective blood levels are rapidly produced. The maximum concentration is achieved within 30 minutes and lasts for about three hours, though high levels are still noted at four hours, and even after this period assayable streptomycin can be detected in the blood. Streptomycin is rapidly excreted in the urine, and, after oral administration, in the feces, but the rate is slower than the rate reported for penicillin. Typical levels maintained in the blood and achieved in the urine, following the intramuscular administration of 0.4 Gm. streptomycin in 4 cc. of physiologic saline every four hours, are presented in Table I.

It will be noted that the dosage used is sufficient to maintain a serum concentration of 4 to 32 mcgm./cc. in the blood serum, with a mean of 16 mcgm./cc. In urine, on an average fluid intake of 2,500 to 3,000 cc. per day, the streptomycin level varies from 400 to 1,200 mcgm. per cc. If the fluid intake is restricted, these levels may be doubled. On the contrary, if renal function is impaired, low urine levels and high blood serum levels are obtained.

The distribution of streptomycin in the body was determined in three cases in which death occurred during the course of treatment. Representative slices of various organs were ground, and the streptomycin was extracted with isotonic saline solution. In addition, assays were made on blood and bile obtained after death. The findings, briefly, are as follows:

(a) Streptomycin was recovered from the bile in one-quarter the concentration present in blood serum. Similar results were obtained on assay of simultaneous samplings of blood serum and bile draining through choledochostomy tubes in two patients.

(b) Pericardial fluid, pleural transudate and ascitic fluid contain one-quarter to one-half of the blood serum level. Studies on patients with ascites suggest that the streptomycin level achieved with a given dosage in the peritoneal fluid depends on the amount of dilution. Streptomycin does not diffuse readily from the blood stream into cerebrospinal fluid. Direct injections are necessary to achieve therapeutic concentrations.

(c) The kidney, liver, muscle and thyroid yield clinically significant amounts of streptomycin, while no assayable streptomycin is found in lymph nodes, spleen, testis, brain and lung parenchyma. Traces only are detected in the prostate and pancreas. Prostatic fluid obtained from six living subjects under treatment with streptomycin contained none of the drug. The findings seem to explain our failures in the treatment of chronic lesions of the prostate due to susceptible organisms, even with relatively large doses of streptomycin administered parenterally.

Pus obtained from thick-walled soft-tissue abscesses was tested for streptomycin in four cases, all with negative results. From these findings it is reasonable to assume that the parenteral administration of streptomycin, like the parenteral administration of other drugs, will neither sterilize abscesses nor cause them to disappear. Streptomycin activity is not influenced by pus, except mechanically.

4. *Susceptibility of Bacteria to Streptomycin.*—The mean blood serum level of 16 mcgm. per cc. which is maintained by the intramuscular administra-

tion of 0.4 Gm. streptomycin every four hours, is the basis for the classification of gram-negative bacteria, as follows:

Inhibition by 4 mcgm./cc. streptomycin—Very sensitive.

Inhibition by 16 mcgm./cc. streptomycin—Sensitive.

TABLE II

ANTIBACTERIAL ACTION OF STREPTOMYCIN: GRAM-NEGATIVE ORGANISMS

Organisms and Total Number of Strains	Streptomycin Mcgm./Cc.*								
	0.5	1	2	4	8	16	32	64	128
<i>Aerobacter aerogenes</i> (53)	..	3	10	14	10	5	2	4	5
<i>Alcaligenes fecalis</i> (1)	1
<i>Brucella melitensis</i> †..... (9)	5	2	1	1
<i>Chromobacterium indicum</i> (1)	1
<i>Chromobacterium violaceum</i> (1)	1
<i>Eberthella pyogenes</i> (1)	1
<i>Eberthella typhosa</i> (12)	..	2	2	4	3	1
<i>Escherichia coli</i> (60)	..	2	11	16	19	7	4	..	1
<i>Hemophilus influenzae</i> †..... (3)	..	1	2
<i>Paracolon group</i> (32)	7	6	11	6	..	1	1
<i>Klebsiella pneumoniae</i> , Type-A.... (28)	..	2	9	11	4	..	1	..	1
<i>Klebsiella pneumoniae</i> , Type-B.... (23)	10	5	3	5
<i>Klebsiella pneumoniae</i> , no type.... (19)	..	2	4	4	5	2	..	1	1
<i>Neisseria catarrhalis</i> (4)	..	2	1	1
<i>Pasteurella avicida</i> †..... (2)	2
<i>Pasteurella bovisepitica</i> †..... (1)	1
<i>Pasteurella equiseptica</i> †..... (1)	..	1
<i>Pasteurella oviseptica</i> †..... (2)	2
<i>Pasteurella pestis</i> †..... (2)	2
<i>Pasteurella stulla</i> †..... (1)	1
<i>Proteus mirabilis</i> (1)	1	..
<i>Proteus morganii</i> (57)	..	1	2	7	20	7	4	5	11
<i>Proteus vulgaris</i> (121)	8	13	55	32	7	4	2
<i>Pseudomonas aeruginosa</i> (98)	2	5	29	33	10	4	15
<i>Salmonella aertrycke</i> (1)	1
<i>Salmonella enteritidis</i> (3)	2	..	1
<i>Salmonella para A</i> (4)	1	3
<i>Salmonella para B</i> (5)	2	1	2
<i>Salmonella pullorum</i> (2)	2
<i>Salmonella typhimurium</i> (1)	1
<i>Serratia marcescens</i> (2)	1	1	..
<i>Shigella dysenteriae</i> Shiga..... (3)	1	..	2
<i>Shigella paradyserteriae</i> (5)	4	1
Total..... (559)	7	18	77	95	171	95	32	21	43

* One microgram = 1 "S" unit.

† Test broth enriched with blood.

No inhibition by 16 mcgm./cc. streptomycin—Insensitive.

No inhibition by 128 mcgm./cc. streptomycin—Resistant.

This classification also applies to infections involving the genito-urinary tract despite the fact that streptomycin is excreted in high concentrations in the urine.⁸ Experience with the treatment of over 350 cases of urinary tract infections has shown that bacteria which grow in a concentration of 16 mcgm./cc. are rarely eradicated from the urine.

Tables II and III present the *in vitro* sensitivities to streptomycin of 559 gram-negative and 452 gram-positive bacteria. Eight hundred forty-six

cultures were isolated from infections observed in the course of this study, and 165 were from a stock culture collection of bacteria.* Our studies showed that the over-all susceptibilities were the same for bacteria freshly isolated from human sources and for bacteria cultivated on artificial media for prolonged periods of time. For this reason they are listed together. These tests, in general, indicate that:

TABLE III

ANTIBACTERIAL ACTION OF STREPTOMYCIN: GRAM-POSITIVE ORGANISMS

Organism and Total Number of Strains	Streptomycin Mcgm./Cc.*							
	0.5	1	2	4	8	16	32	64 128
<i>Bacillus anthracis</i> (4)	4
<i>Bacillus cereus</i> (1)	1
<i>Bacillus megatherium</i> (1)	1
<i>Bacillus mesentericus</i> (1)	..	1
<i>Bacillus mycoides</i> (4)	2	1	1
<i>Bacillus novus</i> (1)	1
<i>Bacillus subtilis</i> (10)	1	2	1	..	4	2
<i>Corynebacterium diphtheriae</i> †..... (2)	1	1
<i>Diphtheroid bacilli</i> (73)	25	9	8	2	1	..	2	1 25
<i>Diplococcus pneumoniae</i> †..... (10)	7	2	1
<i>Micrococci</i> (5)	3	2
<i>Staphylococcus albus</i> (6)	2	..	2	1	1
<i>Staphylococcus aureus, hemolytic</i> (150)	43	31	11	18	8	5	5	2 27
<i>Staphylococcus aureus, nonhemolytic</i> . (12)	6	2	1	3
<i>Streptococcus hemolytic</i> †..... (36)	1	4	2	10	9	5	1	4 ..
<i>Streptococcus nonhemolytic</i> (73)	9	1	3	15	5	25	6	.. 9
<i>Streptococcus viridans</i> (63)	7	4	3	5	14	13	9	1 7
Total..... (452)	102	56	42	56	43	48	23	8 74

* One microgram = 1 "S" unit.

† Test broth enriched with blood.

(a) Streptomycin effectively inhibits the growth of a wide variety of aerobic gram-negative and gram-positive microorganisms. However, the range of sensitivity in both groups is wide, and considerable within species variation is a common feature. The practical need for routine determinations of susceptibility of bacteria in conjunction with therapy is apparent.

(b) Most strains of *Brucella melitensis*, *Eberthella typhosa*, *Escherichia coli*, *Hemophilus influenzae*, *Klebsiella pneumoniae* Type-A, *Pasteurella*, and *Shigella*, *dysenteriae* and *paradysenteriae*, are inhibited by 16 mcgm./cc. of streptomycin.

(c) Resistant strains of bacteria are frequently encountered among *Aerobacter aerogenes*, *Klebsiella pneumoniae* Type-B, *Proteus* and *Pseudomonas*. It may be assumed that resistant members will be found in all groups when large numbers of strains have been checked.

(d) Most aerobic sporulating gram-positive rods are very sensitive to streptomycin. Attention is directed to *B. anthracis*, four different strains having been found inhibited by 0.5 mcgm. of streptomycin per cc.

* Obtained through the courtesy of Dr. H. E. Morton, University of Pennsylvania School of Medicine.

(e) Diphtheria bacilli are sensitive to streptomycin, while Diphtheroids may be very sensitive or highly resistant.

(f) Pneumococci are uniformly inhibited, regardless of serologic type. There is little difference in susceptibility between "S" (smooth) and "M" (mucoid) colony forms.

(g) Staphylococci and streptococci exhibit a wide variation in sensitivity. Staphylococci show no distinction in their susceptibility to streptomycin irrespective of their coagulase or hemolytic properties. Streptococci in their susceptibility to streptomycin show no distinction as relates to their red cell reaction, or the serologic grouping of the hemolytic variety.

SUSCEPTIBILITY OF CLOSTRIDIA AND FUNGI

Not listed in the tables are results of tests on the following *Clostridia*, which were grown in media rich in reducing substances (thioglycollate, brain-heart infusion): *Cl. botulinum*, Types-A and B, *Cl. butyricum*, *Cl. histolyticum*, *Cl. novyi*, *Cl. putrificum*, *Cl. septicum*, *Cl. sporogenes*, *Cl. welchii*, and *Cl. tetani*. All were found insensitive. In addition, two strains each of the fungi, *Candida albicans* and *Saccharomyces cerevisiae*, grew uninhibited in the presence of 128 mcgm. per cc. of streptomycin.

EFFECT OF BLOOD ON SUSCEPTIBILITY OF GRAM-POSITIVE COCCI

It was observed that the *staphylococcus* "SM" strain, which is inhibited by 0.5 mcgm. per cc. streptomycin in the test broth, requires 4 mcgm. per cc. when blood is added. Table IV compares the *in vitro* action of gram-positive

TABLE IV
COMPARISON OF STREPTOMYCIN SENSITIVITY IN PLAIN, MODIFIED
AND BLOOD-ENRICHED MODIFIED F.D.A. BROTH

Organism	F.D.A.	F.D.A.	
		3%	Blood
<i>B. subtilis</i>	<0.5		1
<i>B. anthracis</i>	<0.5		<0.5
<i>B. anthracis</i>	<0.5		1
<i>Staph. aureus</i>	2		8
<i>Staph. aureus</i> "SM".....	0.5		4
<i>Strep. gamma</i>	8		64
<i>Strep. gamma</i>	8		64
<i>Aerogenes-Fried</i>	64		64
<i>Proteus vulgaris</i>	4		8
<i>E. coli</i>	8		4
<i>Ps. aeruginosa</i>	64		64
<i>E. typhosa</i>	2		2

and gram-negative bacteria in the test broth with the same medium containing 3 per cent citrated human blood. It will be noted that the effect of streptomycin on gram-positive cocci is reduced four to eight times in the presence of blood, while the inhibition of gram-negative and gram-positive bacilli is unaltered. Identical results are obtained if 10 per cent human serum or plasma is substituted for whole blood. For this reason, we consider these organisms susceptible only when they are inhibited in the test broth by 4 mcgm./cc. of streptomycin, or in blood enriched broth by 16 mcgm./cc. of streptomycin.

5. *Comparison of In Vitro Action of Streptomycin and Penicillin on Gram-positive Cocci.* The results of a comparative study of the susceptibility of 250 cultures of gram-positive cocci to both penicillin and streptomycin are presented in Table V. The high incidence of penicillin refractory strains of gram-positive cocci* emphasizes the need for an alternative chemotherapeutic agent.

TABLE V

COMPARISON OF IN VITRO ACTION OF STREPTOMYCIN AND PENICILLIN ON GRAM-POSITIVE COCCI

Organism and Number of Strains	Penicillin Sensitivity Oxford U/Cc.	Streptomycin Sensitivity Mcgm./Cc.*								
		0.5	1.0	2.0	4	8	16	32	64	128+
<i>Staph. albus</i> (3)	0.156	1	2
<i>Staph. albus</i> (3)	>2.5	1	2
<i>Staph. aureus, nonhem</i> ... (3)	0.078	2	..	1
<i>Staph. aureus, nonhem</i> ... (2)	0.156	1	1
<i>Staph. aureus, nonhem</i> ... (1)	0.312	1
<i>Staph. aureus, nonhem</i> ... (1)	0.625	..	1
<i>Staph. aureus, hemolytic</i> (11)	>2.5	5	4	2
<i>Staph. aureus, hemolytic</i> (1)	0.019	..	1
<i>Staph. aureus, hemolytic</i> (2)	0.039	1	1
<i>Staph. aureus, hemolytic</i> (3)	0.078	1	2
<i>Staph. aureus, hemolytic</i> (7)	0.156	3	2	1	..	1
<i>Staph. aureus, hemolytic</i> (3)	0.312	1	2
<i>Staph. aureus, hemolytic</i> (2)	0.624	2
<i>Staph. aureus, hemolytic</i> (3)	1.25	..	2	1
<i>Staph. aureus, hemolytic</i> (2)	2.50	2
<i>Staph. aureus, hemolytic</i> (103)	>2.5	24	22	14	16	4	3	1	1	18
<i>Strep. viridans, alpha</i> ... (5)	0.078	..	1	3	1
<i>Strep. viridans, alpha</i> ... (1)	0.156	1
<i>Strep. viridans, alpha</i> ... (1)	0.312	1
<i>Strep. viridans, alpha</i> ... (1)	0.625	1
<i>Strep. viridans, alpha</i> ... (7)	0.125	1	3	1	1	1
<i>Strep. viridans, alpha</i> ... (47)	>2.5	3	2	2	4	11	10	9	..	6
<i>Strep. hem., beta</i> (1)	0.009	1
<i>Strep. hem., beta</i> (1)	0.156	..	1
<i>Strep. hem., beta</i> (2)	0.039	2
<i>Strep. hem., beta</i> (1)	0.625	1
<i>Strep. hem., beta</i> (2)	0.125	1	1	..
<i>Strep. hem., beta</i> (12)	>2.5	..	1	..	2	4	3	2
<i>Strep. nonhem.-gamma</i> ... (3)	0.625	1	1	1
<i>Strep. nonhem.-gamma</i> ... (1)	2.5	1
<i>Strep. nonhem.-gamma</i> ... (15)	>2.5	1	1	1	6	3	..	3
Total..... (250)	45	43	19	28	29	28	16	2	40

* One mcgm. = 1 "S" unit.

It will be noted that, generally, penicillin indifferent cocci are streptomycin-sensitive, and *vice versa*. Twenty-nine of 119 strains of staphylococci (24 per cent) were resistant to both antibiotics. Twenty-three of 74 strains of streptococci (31 per cent) were likewise resistant to both antibiotics. The remaining organisms were mutually susceptible. The findings of a 76 per cent susceptibility rate of penicillin-resistant staphylococci to streptomycin, and a 69 per cent susceptibility rate of penicillin-resistant streptococci to streptomycin, strongly favor a therapeutic trial of streptomycin, if warranted by the clinical and labo-

* These were isolated from patients on prolonged courses of penicillin.

ratory findings. We have demonstrated that subinhibitory amounts of streptomycin and penicillin combined are cumulative in effect. There may be an advantage to administering both drugs simultaneously in selected cases.

6. *Dosage.* As the result of our correlative studies of the clinical and laboratory properties of streptomycin, the following principles have been evolved for determining dosage schedules:

(1) Infections due to bacteria which grow uninhibited in the presence of 16 mcgm./cc. of streptomycin are usually not influenced, regardless of the amount of drug administered.

(2) Doses of 0.5 Gm. of streptomycin administered intramuscularly every four hours maintain blood serum levels in excess of 16 mcgm./cc.

(3) There is no evidence that additional benefits accrue from doses in excess of 3 Gm. a day parenterally administered, regardless of the type and severity of infection.*

(4) The severity of untoward reactions is related to the size of the dose and the duration of therapy.

(5) The anatomic location of the lesion, and the concentration of streptomycin attainable at the site, govern the dosage and mode of administration.

Parenteral Administration.—In the treatment of infections including bacteremia, pneumonia, peritonitis, and acute cellulitis, 3 Gm. per day, in divided doses, is adequate, provided the organisms are susceptible *in vitro*, and adequate levels can be reached in the affected tissue. Two grams per day are usually sufficient in the treatment of infections of the urinary tract, and of specific infections, such as tularemia. Regardless of dosage, adequate drug levels are not possible in poorly vascularized tissues.

Local Administration.—Local administration of streptomycin is necessary in the treatment of infections of the ear, meninges, brain, pleura, and tracheo-bronchial tree. The dosage employed varies from 50 to 250 mg., dissolved in an appropriate amount of sterile isotonic saline.

Oral Administration.—Oral administration is required for the treatment of intra-enteric infections. A dosage of 1 Gm. every eight hours, in water, is optimum.

7. *Drug-fastness.*—Bacteria rapidly acquire habituation to doses of streptomycin which were originally lethal. This phenomenon is most commonly observed during the treatment of urinary infections, and occurs either when sublethal doses of the drug are employed or with lethal concentrations of the drug in the presence of nonsterilizable foci of infections. The development of drug-fastness may be extraordinarily rapid, occurring in the urinary tract with as little as two days of therapy. Once it occurs, drug-fastness is irreversible, and drug-fast bacteria reproduce drug-fast bacteria. The change is specific and does not indicate concomitant resistance to other chemotherapeutic agents. Table V showed most streptomycin-resistant strains of gram-positive cocci are susceptible to penicillin and *vice versa*. The two agents may be used simul-

* This statement is based on accumulated experience with 1,000 streptomycin-treated cases of infection in U. S. Army Hospitals.

taneously if the clinical course of the disease warrants. One agent can be substituted for the other if maximum effects are not achieved within a few days by the one first employed.

SUMMARY

1. One thousand cultures of bacteria were tested for their susceptibility to streptomycin by a broth-serial-dilution method. The results are tabulated.
2. Data are presented on results of studies on absorption, distribution, and excretion of streptomycin in the body following parenteral administration of the drug.
3. The results of susceptibility tests and of assays of blood serum concentrations of streptomycin have been correlated. On this basis a division between clinically-sensitive and clinically-refractory bacteria is made.
4. The *in vitro* action of streptomycin and penicillin on 250 strains of gram-positive cocci is compared.
5. The principles which govern dosage are outlined.
6. Certain data on drug-fastness are presented.

The authors are grateful to Gen. Ralph G. DeVoe, M. C., U. S. Army; Col. E. N. Packard, M. C., of the Halloran General Hospital; and to Col. Michael E. DeBakey, M. C., Acting Director, Surgical Consultants Division, Office of the Surgeon-General, for their valuable assistance and coöperation in establishing the streptomycin study-unit.

REFERENCES

- ¹ Donovan, R., Hamre, D., Davanagh, F., and Rake, G.: A Broth Dilution Method of Assaying Streptothricin and Streptomycin. *J. Bact.*, 50, 623-628, December, 1945.
- ² Price, G. W., Neilsen, J. K., and Welch, H.: Estimation of Streptomycin in Body Fluids. *Science*, 103, 56-57, January 11, 1946.
- ³ Adcock, J. D., and Hettig, R. A.: Absorption, Distribution and Excretion of Streptomycin. *Arch. Int. Med.*, 77, 179-195, February, 1946.
- ⁴ Anderson, D. G., and Jewell, M.: The Absorption, Excretion and Toxicity of Streptomycin in Man. *New England J. Med.*, 233, 485-491, October, 1945.
- ⁵ Buggs, C. W.; Pilling, M. A.; Bronstein, B., and Hirshfield, J. W.: The Absorption, Distribution and Excretion of Streptomycin in Man. *J. Clin. Investigation*, 25, 94-102, January, 1946.
- ⁶ Heilman, D. H., Heilman, F. R., Hinshaw, H. C., Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion and Toxicity. *Am. J. M. Sc.*, 210, 576-584, November, 1945.
- ⁷ Zintel, H. A., Flippin, H. F., Nichols, A. C., Wiley, M. M., and Rhoads, J. E.: Studies on Streptomycin in Man: I. Absorption, Distribution, Excretion and Toxicity. *Am. J. M. Sc.*, 210, 421-430, October, 1945.
- ⁸ Pulaski, E. J., and Amspacher, W. H.: Streptomycin Therapy in Urinary Tract Infections. In press.

(Part II of this article—Streptomycin in Surgical Infections: Infections of the Genito-urinary Tract, appeared in the *ANNALS OF SURGERY*, 124, 392, August, 1946.)

SYMPATHECTOMY IN TRENCH FOOT

LT. COL. HARRIS B. SHUMACKER, JR., M.C.,
NEW HAVEN, CONN.

AND

MAJOR DAVID I. ABRAMSON, M.C.
CHICAGO, ILL.

FROM THE VASCULAR CENTER, MAYO GENERAL HOSPITAL, GALESBURG, ILLINOIS.

TRENCH FOOT is a syndrome which follows prolonged exposure of the feet to a wet and cold environment. In contrast to frostbite, it often occurs in weather which is not freezing. The moisture of the shoes and socks renders the limb more susceptible to thermal injury, since it reduces or eliminates the phenomenon of supercooling in tissues.¹ Moisture also facilitates heat loss from the foot and more effective transmission of cold to the body. The initial response of the blood vessels in the limb to such environmental conditions is marked vasoconstriction, and, as this persists, the resistance of the tissues to the trauma of cold diminishes. The cramped position in the slit-trench or other emplacement and the absence of muscular movements also contribute to the decrease in circulation.

The physiologic and pathologic alterations in the foot may result in actual necrosis of tissue, or, if this does not occur, there may still be loss of nails, the production of vesicles, or desquamation of skin. Even in the absence of gangrene, extensive damage to muscles and nerves may take place, followed by fibrosis, atrophy, contractures, sensory disturbances, and pain on weight-bearing. The intense vasospasm observed initially may be replaced by a transient period of hyperemia, and subsequently, in most instances, by the return and persistence of excessive sympathetic tonus.

Since vasoconstriction is, therefore, one of the fundamental factors in the pathogenesis of trench foot and also one of the most common sequelae, it is important to inquire into the therapeutic effect of such a procedure as sympathectomy, which is capable of completely eliminating the hypertonus. It is the purpose of this communication to present the data obtained following the use of lumbar sympathectomy in the treatment of trench foot and to discuss its applicability and limitations.

USE OF SYMPATHECTOMY IN THE EARLY TREATMENT OF TRENCH FOOT

Little information is available concerning the use of lumbar sympathectomy in the treatment of the early stage of trench foot. Edwards, and his associates² have studied the problem in 13 patients and have come to the conclusion that the results are good in those individuals with gangrene, but that the procedure did not help those with tender, painful, aching feet of the swollen, warm, and nonswollen types.

We have had no personal experience with this problem, but have had the opportunity subsequently to observe two patients in whom this procedure was performed during the first few weeks after exposure. One of these was con-

vinced that the operation had aided in healing his gangrenous toes, although when he was seen by us eight months later, two tiny ulcers had recurred which healed readily with warm compresses. The second patient had undergone a left lumbar sympathectomy 30 days after exposure, and this had resulted in a warm, dry foot, with some decrease in edema but no effect upon the pain.

SYMPATHECTOMY IN THE LATER TREATMENT OF TRENCH FOOT

Approximately 700 patients with trench foot were admitted to the Vascular Center at the Mayo General Hospital during the period from June, 1944, to October, 1945, and of this number, 49 were subjected to sympathectomy. In all, 66 lower extremities were sympathectomized. In every instance, under spinal anesthesia, the second and third lumbar sympathetic ganglia with the intervening chain were excised through an anterior extraperitoneal approach. No complications occurred. In many patients the operation was preceded by a procaine lumbar sympathetic block, in order to obtain some information as to the possible effects of sympathetic denervation on the clinical manifestations. The results with this procedure were utilized in making a decision as to whether or not sympathectomy would be of any therapeutic value.

The following data have been segregated into three groups according to the chief indication for operation; namely, (1) the presence of extensive gangrene; (2) the existence of excessive sympathetic tonus; and (3) the complaint of pain on weight-bearing. In addition, the effect of sympathectomy on the neurologic and certain other manifestations of trench foot has been evaluated in a separate section.

PATIENTS WITH DEEP GANGRENE

Thirty patients in the series had deep gangrene, and in all, 38 lumbar sympathectomies were performed upon them. The operation was done within one to two months after exposure in the case of 16 individuals, two to three months in ten, and 3.5 to eight months in the remaining four (Table I).

Infection was present in all cases except one, while in 26 individuals there was obvious evidence of excessive sympathetic tonus, with coldness, cyanosis, and hyperhidrosis. These findings were sometimes masked by the local heat resulting from the associated infection. In 16 extremities complete gangrene of one to five toes was present while in 35, portions of toes were involved. In 13 limbs removal of the gangrenous tissue left the heads of one, or more, metatarsal bones exposed. Five of the patients had ulcers of the heel or foot. All but three were bedridden when admitted to the hospital.

Generally, at the same time that the sympathectomy was performed the gangrenous parts were amputated through the line of demarcation, and subsequently débridement, revision of stumps, small deep, split-thickness and tube-transfer grafts were carried out, as indicated in Table I. In only one instance (Case 2) was it feasible to perform an amputation with primary closure. In all other patients, infection presented a difficult problem, not because of its spread into adjacent soft tissues but because it interfered with skin grafting or had produced osteomyelitis of the stumps. In most instances the

SYMPATHECTOMY IN TRENCH FOOT

infection was mixed in type. Among the organisms found were various sulfonamide- and penicillin-sensitive bacteria but frequently also resistant *B. proteus* and *B. pyocyaneus*. As a general rule, sulfadiazine or penicillin was given on admission, and all patients were treated with warm sterile saline compresses applied locally.

Results.—Following sympathectomy the infection generally cleared up rapidly, and satisfactory healing occurred in all cases. In those instances in which the metatarsal bones were exposed and skin grafts were necessary, the period for complete healing was increased. The average duration of hospitalization after sympathectomy was 4.5 months, but this gives no index as to the rate of healing, since a sick leave of three or four weeks and a regimen of reconditioning were part of the routine program for each patient.

TABLE I
DATA ON PATIENTS WITH GANGRENE TREATED BY SYMPATHECTOMY

Case No.	Sympathectomy, Months After Exposure	Extent of Gangrene			Amputation and Plastic Procedures	Effect of Sympathectomy on Neurologic Signs		Pain on Weight-Bearing After Operation
		Part of Toes; No. Involved	Entire Toe; No. Involved	Metatarsal Heads Exposed; No. Involved		Hypoesthesia	Hyperesthesia	
1	L-5		L-4	L-3*	AO; RA			Moderate
2	R-8	R-1			AC	Relieved		Slight
3	R-7	R-2			AO; RA; SG			Moderate
4	L-2	L-3			E			Slight
5	R-2; L-2.5	R-2; L-2	R-2; L-1	R-1; L-1	AO			Slight
6	R-1.5; L-2	R-1	R-3; L-3	R-1; L-1*	AO; TG			Slight
7	L-2	L-2			E	Relieved		Slight
8	R-2	L-2	R-3	R-1*	AO; SG	Relieved		Moderate
9	R-2; L-2.5	R-4; L-4			E		Relieved	Moderate
10	R-2	R-2			E			Moderate
11	R-2; L-2	R-4; L-1	R-1	R-1*	AO; FG			Moderate
12	R-3	R-1	L-2	L-1*	AO; PG; SG	No change	No change	Moderate
13	R-2; L-2		R-5; L-5	R-4; L-2	AO; TG; SG			Slight
14	L-1; R-1.5	R-1	L-5; R-4		AO; SG	Relieved		Moderate
15	L-2.2	L-1			E	No change		Moderate
16	L-2	L-2	L-2		AO; SG	Relieved		Slight
17	R-2.2	R-2			E; AC; SG			Moderate
18	L-1.5	L-5; R-1			AO; SG			Slight
19	L-2.2	R-5			AO; SG			Moderate
20	L-2.2	R-2	L-5	L-4*	AO; TG; SG	Relieved		Moderate
21	R-2	R-5; L-3			AO			Moderate
22	L-2.3	L-1			E	Relieved		Moderate
23	R-2.5	R-5			E; AO	Improved		Slight
24	L-1	L-2			AO; SG			Slight
25	L-2.5; R-3.3	R-5; L-5			AO; SG; RA		No change	Moderate
26	R-1	R-1			E	No change		Moderate
27	L-1.2; R-1.7		R-5; L-5	R-3; L-3*†	AO; SG; TG	Relieved		Slight pain in ankle; none in foot
28	L-1.5	L-4; R-1			E; SG; AC			No pain
29	L-1.5	R-3; L-3			AO; SG; RA			Moderate
30	L-4	L-4			AO; SG; RA		No change	Slight

The symbols used in column 6 (Amputation and Plastic Procedures) are as follows: AO—Amputation with primary closure; AC—amputation with primary closure; RA—reamputation; PG—small deep grafts; SG—split-thickness graft; TG—tube-transfer graft; E—excision of gangrenous plaques.

* Portion of metatarsal heads removed.

† Portion of one metatarsal head removed.

The effect upon the healing of gangrenous ulcers through increasing the circulation by sympathectomy is illustrated in Case 1 (Table I). The patient had been admitted to the hospital with an infected granulating stump from which the first four toes had been amputated four months previously. After treating the infection, small deep grafts were applied, but these were not successful. Since the foot was cold, wet and cyanotic and little epithelization had occurred during all the months of hospitalization, it was decided to perform a sympathectomy. Within a few days after operation healing was complete. The stump was subsequently revised because the skin over the distal end of the foot was delicate and thin.

TABLE II
SYMPATHECTOMY IN PATIENTS WITH EXCESSIVE SYMPATHETIC ACTIVITY
Manifestations Before Operation

Case No.	Date Exposure	Date, Sympathec- tomy, Side	Finding in Ordinary Environment	Result of Ex- posure to Cold	Effect of Sympathectomy
1	June '43	8/2/44 R	Coldness, cyanosis, hyperhidrosis; numbness rt. leg and both feet; recurrent ulcers rt. foot; conversion hysteria	Intense coldness and numbness	Foot warm, dry and of good color; no discomfort; ulcers healed
2	Feb. '44	4/3/44 R* 10/17/44 L	Coldness, hyperhidrosis and burning and tingling lt. foot on walking; healed stumps, rt. 2, 3, 4, 5 toes; healed gangrene lt. 5th toe	Coldness in- creased	Rt. sympathectomy had aided healing of gangrenous toes. After lt. sympathectomy foot warm, dry and without cold sensitivity or pain on weight-bearing
3	Dec. '43	10/25/44 L	Severe hyperhidrosis, especially lt. foot, with maceration of skin and secondary infection, coldness and cyanosis; slight pain on weight-bearing	Coldness and cyanosis in- creased	Foot warm, dry and of good color; skin lesions healed; on exposure to cold no pain in lt. foot but still present in rt.; pain on weight-bearing unchanged
4	Feb. '44	12/16/44 L 12/21/44 R	Coldness, cyanosis, marked hyperhidrosis; pain on weight-bearing	Pain in feet; in- creased coldness and cyanosis	Feet warm, dry and of good color; reduction in pain on exposure to cold; pain on weight-bearing unchanged
5	Nov. '43	1/13/45 L 1/27/45 R	Coldness, cyanosis and marked hyperhidrosis with maceration of skin and secondary infection; some edema; throbbing and burning pain on walking	Tingling pain, both feet	Feet warm, dry and of good color, throbbing pain gone; edema improved; burning; pain on walking unchanged
6	Dec. '43	1/5/45 R 2/1/45 L	Coldness, cyanosis and hyperhidrosis; throbbing rest pain; pain on weight-bearing; hypesthesia	Coldness, ach- ing and throbbing increased	Feet warm, dry and of good color; cold sensitivity partially relieved; throbbing pain and hypesthesia gone; pain on weight-bearing unchanged
7	Dec. '43	1/29/45 R	Hyperhidrosis, coldness and cyanosis; mild pain on weight-bearing	Coldness in- creased	Foot warm and dry; pain on weight bearing unchanged
8	Nov. '44	3/23/45 L	Pain on weight-bearing; some edema; uncomfortable hypesthesia	Coldness and numbness	Cold sensitivity relieved, edema, pain and hypesthesia unchanged
9	Dec. '44	7/23/45 L 8/2/45 R	Coldness, cyanosis and hyperhidrosis; slight pain on walking; healed superficial gangrene	Marked cold- ness, aching, tingling and burning pain	Complete relief of coldness, hyperhidrosis and cold sensitivity; pain on weight-bearing little if any better

* Performed in hospital overseas and not analyzed in present series.

SYMPATHECTOMY IN TRENCH FOOT

In addition to the case reports in Table I, Case 1 in Table IV had deep gangrene of the plantar surface of both great toes which healed readily following bilateral sympathectomy and excision of the gangrenous portions. Figures 1 to 4 illustrate feet with varying degrees of gangrene and the results following sympathectomy.

PATIENTS SUFFERING FROM EXCESSIVE SYMPATHETIC ACTIVITY

Thirteen sympathectomies were performed on nine patients who were suffering from symptoms resulting from the presence of excessive sympathetic activity. In four individuals (Cases 3, 4, 5 and 7, Table II), the operation was performed chiefly because of otherwise uncontrollable hyperhidrosis which caused considerable distress, kept the socks almost constantly wet, and in two was associated with definite maceration of the skin followed by local infection. All had evidence of epidermophytosis and also definite sensitivity to cold.

In the remaining five cases in this group, sympathectomy was undertaken primarily because of cold sensitivity. All of these individuals developed intense coldness of the feet during exposure to a low environmental temperature, associated in two cases with a distressing sense of numbness and in two others with pain, not otherwise present. Four of these patients also had rather marked hyperhidrosis. In addition, one of them had recurrent superficial ulcers of the foot.

Results.—Following operation every patient in the above group developed warm, dry feet which were much less responsive to cold. The associated discomfort was likewise minimized. In the case of two individuals with maceration of the skin and subsequent local infection, the infection cleared up shortly after sympathectomy. That the sympathectomized limb maintains greater warmth and has better arterial pulsations than the untreated extremity is demonstrated in Table III.

TABLE III

EFFECT OF SYMPATHECTOMY ON SKIN TEMPERATURE OF TOES AND ON OSCILLOMETRY AT ANKLE

Case No.	Oscillometry		Skin Temperature °C.*	
	Nonoperated Limb	Operated Limb	Nonoperated Limb	Operated Limb
1.....	1	2.5	23.5-25	35 -36
2.....	4.5	5.5	18 -19	33.5-35
3.....	2	4.5	21.5-23.5	28 -29
4.....	1.5	4	28 -29	32 -35
5.....	0.75	2.5	19 -22.5	31.5-34
6.....	4	5	25 -25.5	30 -31
7.....	3.5	5.5	24.5	32 -35.2
8.....	3	5	30 -32	33 -35.5
9.....	2.5	4	24 -29	34 -34.5
10.....	1.2	3	21	32
11.....	4.5	5	22.5-23.5	27.5-28.5
12.....	7	9	31	32 -33
13.....	2	4	24	34
14.....	2	5	27.5-28.5	36.5
15.....	0.75	4	27 -27.5	33.5-34.5
16.....	3	4	31 -31.5	34 -34.5
17.....	3	6.5	31.5-33	35.5
Average.....	2.6	4.6	25.8	33.2

* Readings indicate range of temperature in first, third and fifth toes.

PATIENTS SUFFERING FROM PAIN ON WEIGHT-BEARING

Fourteen sympathectomies were performed upon ten patients primarily because of pain in the foot on weight-bearing. This was present either in the metatarsal area or less frequently in the heel. In an attempt to minimize the symptoms, the patient would resort to applying the weight of his body to the nontender portions of the feet. As a result, he walked either on his heels or along the lateral edges of the feet. All of the individuals also showed evidence of fairly marked vasospasm.

TABLE IV

SYMPATHECTOMY IN PATIENTS WITH PAIN ON WEIGHT-BEARING

Case No.	Date Exposure	Date Sympathectomy and Side	Location of Pain	Type of Walking	Other Manifestations	Results
1	Dec. '43	6/12/44 L 6/19/44 R	Metatarsal area	Heel	Gangrene, both great toes; coldness, cyanosis and hyperhidrosis	Normal walking, without pain; gangrene healed; good color and warmth; no sweating
2	Dec. '43	7/21/44 R 8/18/44 L	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis; marked edema after 7.5 months' bed rest; marked hyperesthesia	Pain on weight-bearing unchanged; good color and warmth; no sweating; edema gone; hyperesthesia gone except in distal fourth, both feet
3	Mar. '44	8/9/44 R	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis	Pain on weight-bearing unchanged; good color and warmth; no sweating
4	Mar. '44	4/4/44 L* 8/18/44 R	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis, rt. foot	Original operation made foot warm, dry and of good color and decreased edema. Second had no effect on pain on weight-bearing, made foot warm, dry and well-colored
5	Nov. '43	8/23/44 R	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis	Pain on weight-bearing unchanged; good color and warmth; no sweating
6	May '43	8/30/44 R 9/11/44 L	Heels, ankles and rt. 1st metatarsal head area	Limp	Coldness, cyanosis and hyperhidrosis; slight edema	Complete relief of pain on weight-bearing and of vasospasm
7	Jan. '44	9/22/44 R	Metatarsal area and heel	Limp	Lt. peroneal and rt. tibial paralysis	Pain gone from heel but unchanged in metatarsal area
8	Nov. '43	1/5/45 R 2/12/45 L	Metatarsal area	Limp	Coldness, cyanosis and hyperhidrosis; marked pain on exposure to cold	Walking distance before onset of pain increased from $\frac{1}{2}$ to over 1 to 2 miles; good color and warmth; no sweating; no cold sensitivity
9	May '43	2/1/45 L 2/13/45 R	Heels	Toes; lateral edge of foot	Coldness, some burning rest pain	Almost complete relief; no pain on standing or walking except after very long distances; rest pain almost completely gone; feet warm
10	Nov. '44	7/31/45 L	Lt. metatarsal	Heel	Gangrene, lt. great toe; coldness, cyanosis, hypesthesia, distal fourth, both soles	No pain in foot on weight-bearing; slight pain, lt. ankle, on prolonged walking; gangrene healed; foot warm and of good color; hypesthesia disappeared from both feet

* Performed in hospital overseas and not analyzed in present series.

SYMPATHECTOMY IN TRENCH FOOT

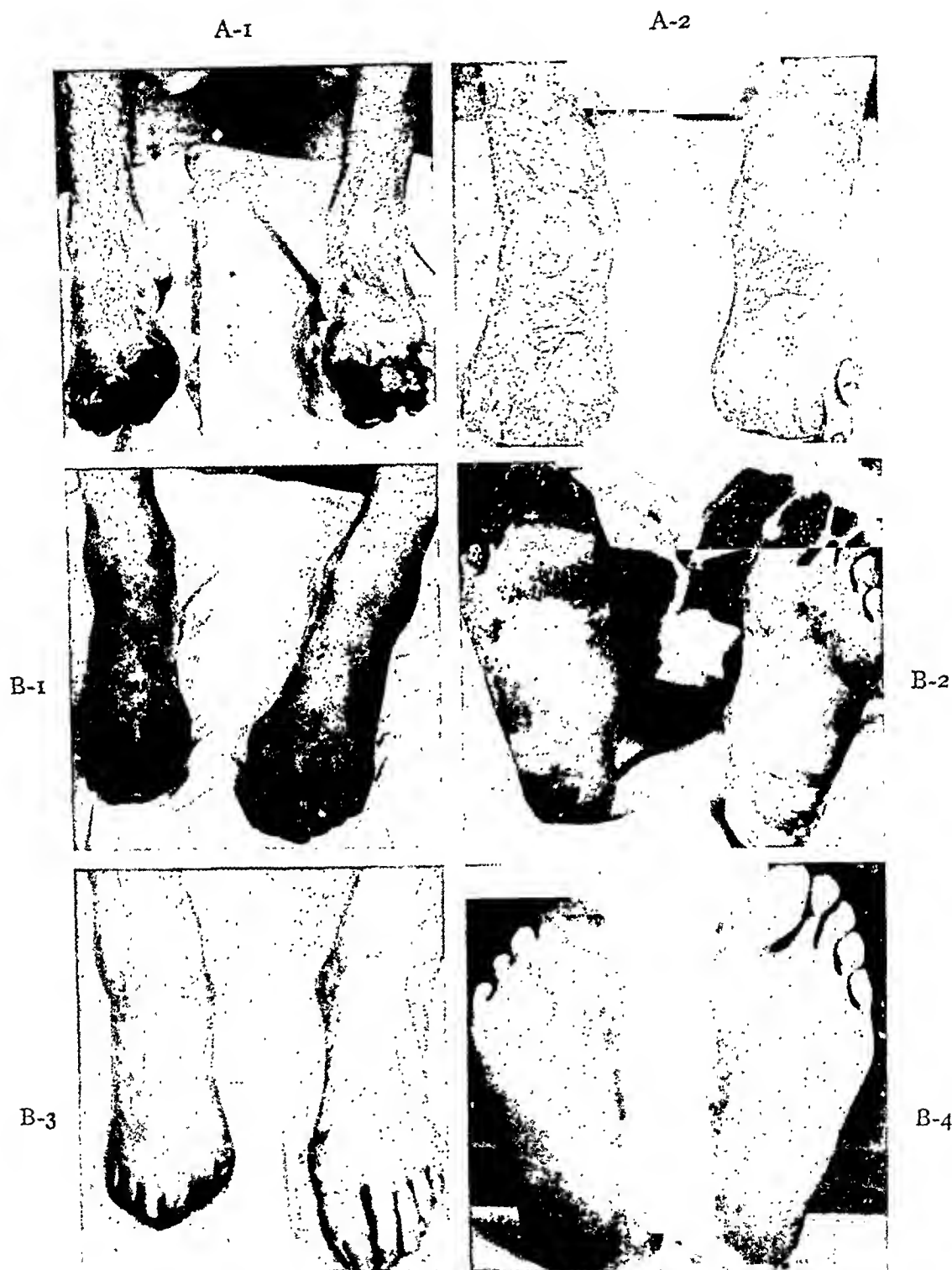


FIG. 1.—Two patients with extensive deep gangrene. A-1, B-1 and B-2, condition originally. A-2, B-3 and B-4, final results following bilateral sympathectomy and amputation. Good functional foot obtained in both cases. Head of the first metatarsal left exposed after amputation in each instance and in Case B, a part of the metatarsal head had to be removed.

Result.—The results following sympathectomy in this group of patients were variable. In the two individuals (Cases 6 and 9, Table IV) in whom the symptoms were limited chiefly to the heels, complete relief in both feet followed the operation. Another patient (Case 7) had pain in one heel and in the meta-

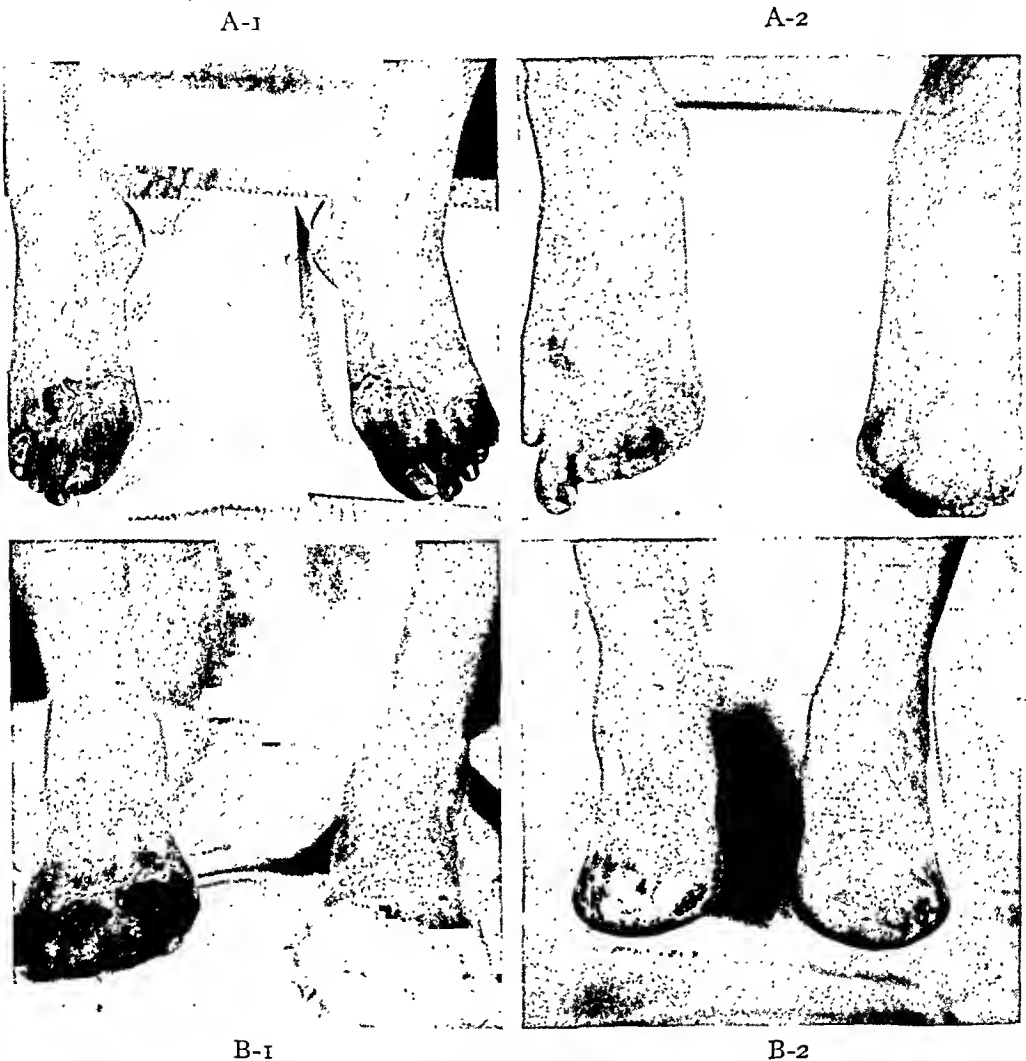


FIG. 2.—Two patients with extensive deep gangrene. A-1 and B-1, condition originally. A-2 and B-2, final results following bilateral sympathectomy and amputation. Satisfactory healing and good functional result obtained. Split-thickness grafts utilized in Case A to aid healing. Heads of both first metatarsals exposed following amputation in Case B, and a transfer-tube graft used to cover the defect of the right foot. The fourth and fifth toes stiff and painful and subsequently amputated.

tarsal area, and, again, relief occurred in the former site. Of the 11 sympathectomized limbs in which there had been pain primarily in the metatarsal area, complete relief occurred after operation in three (Cases 1 and 10), partial relief in two (Case 8), and no change in six (Cases 2, 3, 4, 5 and 7). One of the patients (Case 8) who showed some improvement could now walk one to two miles before pain appeared, whereas previously this distance was only one-eighth-mile, or less.

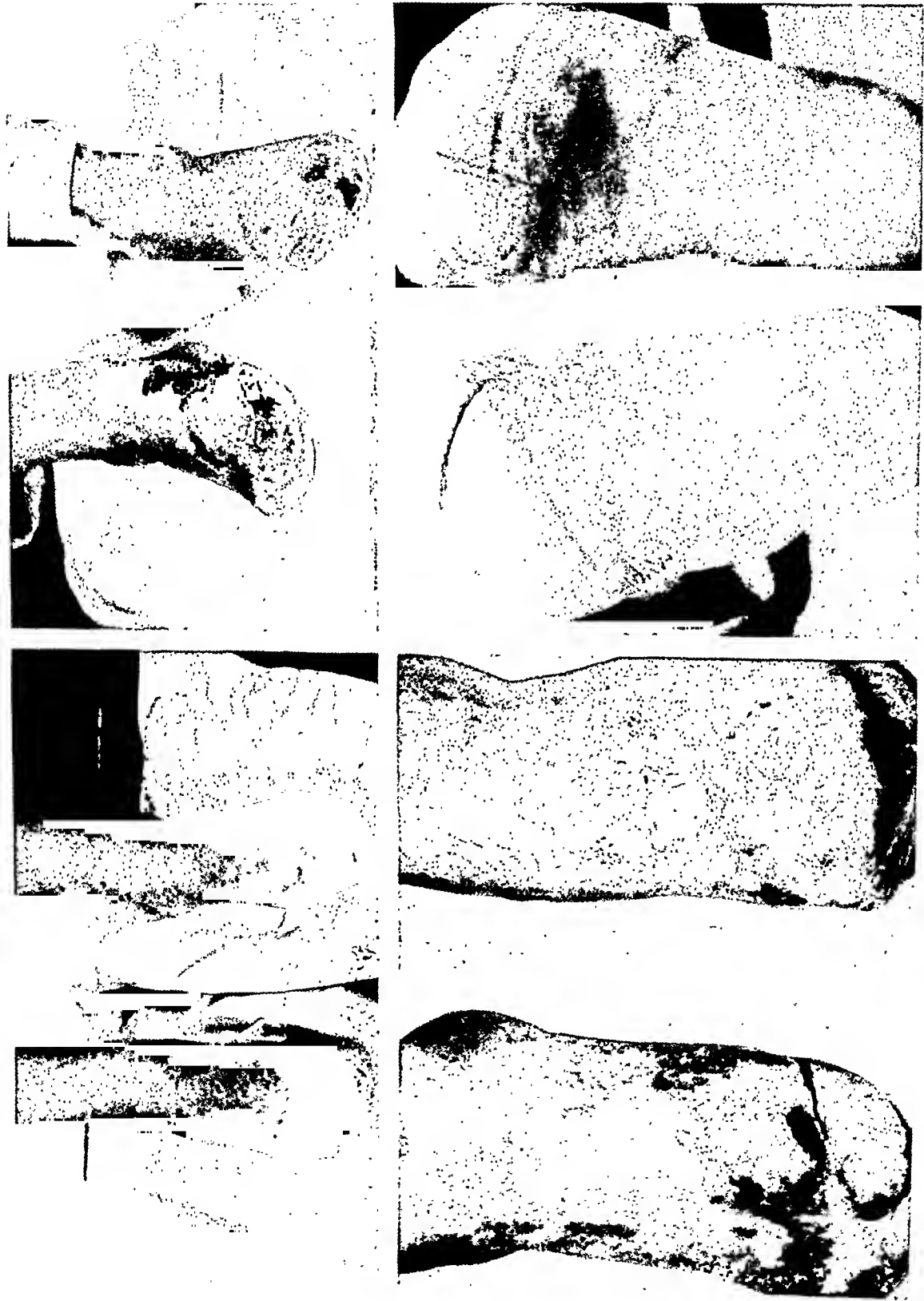


FIG. 3.—Patient with extensive deep gangrene. (A) Condition on admission. (B) After bilateral sympathectomy and amputation. (C and D) The final result. First and third heads of metatarsals on left and the first four on right exposed after amputation. A tube-transfer graft used to cover defect of right foot. A good functional result obtained.

Besides the information obtained from the above group of patients, additional data on the effect of sympathectomy upon the symptoms associated with weight-bearing were collected from the other two groups. Of those cases tabulated in Table II, one individual (Case 2) had burning and stinging pain in the left foot on walking, which disappeared following operation, while in seven, no change was observed postoperatively. Of the three patients listed in Table I who were ambulatory on admission, the discomfort on walking was improved after sympathectomy in one, while in the other two no change was noted. When the remaining 27 patients in the group began to walk again,

A

B



C



D

FIG. 4.—Patient with extensive gangrene. (A and B) Condition after bilateral sympathectomy and amputation. (C and D) The final result. Transfer-tube grafts necessary to cover defect of both feet. The first three metatarsal heads exposed on both feet, and part of the right first metatarsal head removed. A small sequestrum delayed complete healing. Good functional result obtained.

after healing of the lesions had occurred, two experienced no pain in the feet with weight-bearing in the sympathectomized extremities, while nine had slight, and 16 moderate complaints.

PATIENTS WITH NEUROLOGIC AND OTHER DISTURBANCES

In many of the patients in the above three groups, different types of sensory

disturbances were present. These were affected in a variable manner by sympathectomy. In some instances no conclusions could be drawn because of inadequate notes concerning neurologic signs following operation. In those individuals in whom pertinent data were available, hypesthesia was completely relieved in 11 extremities, improved in one, and unchanged in four. Hyperesthesia was relieved in one, improved in two, and unchanged in three. However, it must be stated that some patients, while undergoing no specific treatment, also showed definite improvement or relief of sensory disturbances. Furthermore, in two individuals hypesthesia disappeared from both feet following unilateral sympathectomy.

In a number of the patients in whom there was coincident slight edema of the feet, no significant alteration was noted following sympathectomy. However, in one in whom marked swelling had persisted for nearly eight months of complete bed rest (Case 2, Table IV), spectacular subsidence of the edema occurred within 48 hours after operation. Subsequently there was no recurrence except for slight swelling after prolonged standing or walking.

In practically all of the patients with extensive gangrene and in many of the others without loss of tissue, signs of osteoporosis were noted in the admission roentgenograms. Subsequent films, taken at intervals during the course of the hospitalization, showed no significant difference in bony changes in the sympathectomized as compared with the untreated extremities.

DISCUSSION.—The data presented in this communication substantiate in part the view that in trench foot elimination of excessive sympathetic activity through sympathectomy has a beneficial effect on the course of the disease. It would appear that this operation has a definite place in the care of those patients who are suffering from deep gangrene. However, it must be pointed out that in this study no control series of cases was established and, hence, we have no unequivocal evidence in this regard. Certainly, in the case of superficial gangrene, healing occurs readily and without the benefit of sympathectomy. Nevertheless, it is our general impression that in those individuals with extensive gangrene, in whom there is obvious evidence of vasospasm, sympathectomy will play an important rôle in accelerating the rate of healing of the lesions and in preserving as much tissue as is possible.

Again, for those patients with marked cold sensitivity, associated with extreme hyperhidrosis, maceration of the skin and secondary infection, sympathectomy is a valuable therapeutic aid. In the case of the existence of cold sensitivity alone, the decision as to whether this operation is indicated should depend to some degree upon the type of life the patient is to lead and the climate in which he is to live. Certainly, it should not be considered in the light of a routine procedure in the treatment of this complaint.

Sympathectomy regularly eliminates the signs and symptoms of vasoconstriction and produces a warm, dry limb, of good color. However, it is not felt that vasoconstriction, *per se*, in the absence of annoying symptoms related to it, is sufficient reason to perform the operation. Whether by relieving excessive vasomotor tonus and maintaining almost maximal circulation to a foot, a

more rapid return of the tissues to normal will result can only be determined by follow-up studies. Up to the present, there are insufficient data upon which to base any definite conclusions on this point.

The results of sympathectomy in the treatment of pain on weight-bearing are not clear-cut enough to warrant extensive use of the procedure in this regard. It is of interest, however, that in every instance of pain in the heel, complete relief of symptoms resulted.

With respect to the sensory disturbances, it would seem that sympathectomy is of some benefit. Since these are only of minor importance and certainly are not incapacitating, the operation is not indicated in the treatment of them alone.

In the evaluation of the preliminary use of a procaine sympathetic block to determine the possible effect of removal of sympathetic tonus, our results have at times been misleading. This has been particularly true in an effort to determine whether or not sympathectomy would relieve the symptoms associated with weight-bearing. Several patients who apparently had complete or considerable relief in this regard immediately after procaine sympathetic block, subsequently showed no improvement following sympathectomy. The difference in response may be explained on the possibility that the first lumbar sympathetic ganglion was also anesthetized during the block, while at operation it was routinely left intact. Unfortunately, this matter was not investigated further by studying the effect of anesthetization of this ganglion postoperatively. It is also possible that the patient's desire to be rid of an incapacitating difficulty may have colored and exaggerated his interpretation of any apparent relief of symptoms during the period of the block. In this respect, it can be stated that every effort was made to avoid any promises or encouragement prior to this procedure.

Despite the above experience, we still feel that sympathetic blocks are of value in certain instances in determining the advisability of sympathectomy. For example, in every individual in whom this operation is being contemplated for the treatment of pain on weight-bearing or marked sensitivity to cold, the preliminary results with procaine block should be carefully studied. In all instances in which little or no relief occurs, it is quite likely that sympathectomy will also yield disappointing results. Naturally, preliminary blocks are not necessary in the case of hyperhidrosis, since sympathectomy always eliminates sweating. Furthermore, since improvement in the cutaneous circulation invariably follows permanent removal of vasomotor tonus in patients with trench foot, preliminary procaine blocks are likewise not essential in the case of extensive gangrene with vasospasm. If this information should be required, the response to inhibition of vasoconstrictor impulses can be assayed during spinal anesthesia, before operation is begun.

SUMMARY AND CONCLUSIONS

1. The effect of lumbar sympathectomy in the treatment of the sequelae of trench foot was studied in a series of 66 extremities.

2. It was felt that this procedure played a definite rôle in accelerating the rate of healing of the lesions in patients with extensive gangrene associated with vasospasm.

3. It was also of aid in treating the maceration of the skin and the complicating secondary infection which result in patients with prolonged marked hyperhidrosis.

4. The procedure reduced the severity of the symptoms in those patients suffering from cold sensitivity.

5. It produced variable results in the treatment of pain on weight-bearing, but had some therapeutic effect on the sensory disturbances.

6. It is concluded that sympathectomy has a definite but limited use in the treatment of certain selected cases of trench foot. In the majority of patients it appears to have no applicability as a therapeutic aid.

The authors wish to express their appreciation to Captains P. B. Olsson, R. B. Murray and H. A. Aronson, who helped in the treatment of the patients in this series.

REFERENCES

- ¹ Lewis, T.: Observations on some Normal and Injurious Effects of Cold upon Skin and Underlying Tissues. III Frostbite. *Brit. Med. J.*, 2, 869, 1941.
- ² Edwards, J. C., Shapiro, M. A., and Ruffin, I. B.: Trench Foot: Report of 351 Cases. *Bull. U. S. Army Med. Dept.*, 83, 58-66, 1944.

CONGENITAL DISLOCATION OF THE HIP

M. BECKETT HOWORTH, M.D., D.Sc. (MED.)

NEW YORK, N. Y.

FROM THE COLLEGE OF PHYSICIANS AND SURGEONS OF COLUMBIA UNIVERSITY,
AND THE NEW YORK ORTHOPEDIC HOSPITAL, NEW YORK CITY, N. Y.

EMBRYOLOGY AND INFANT ANATOMY

THE SEARCH for the cause of congenital dislocation of the hip is concerned with the development of the embryo and the fetus, and the best surgical treatment of the condition, whether manipulative or open, is dependent upon a thorough understanding of the anatomy of the infant hip. Textbooks of anatomy and embryology are notably brief and often vague on the anatomy of the infant and the embryology of the hip, while, aside from the work of Strayer,¹ medical literature and the personal communications of those familiar with the embryology of other portions of the body are of little assistance here. Because of these considerations a study of the hip joints of available fetuses has been made.

There were 15 specimens ranging in fetal age between ten weeks and full term. As no hip with congenital dislocation was found in this group or could be located in the laboratories or museums of the Columbia University Medical Center in New York, the study was confined to normal hips. The muscles surrounding the hip joint were dissected in detail in the larger specimens, and the capsule of the joint, the femur and the innominate bone were studied in all instances. Dissections were made from various approaches in order to study various portions of the joint without disturbing them. Slides were made of sections from several of the hips and studied microscopically, but as these observations are irrelevant they will not be included here. Roentgenograms were made of the innominate bone and articulated femur in several instances.

The youngest femur measured 2 cm. over-all, and was estimated to be ten weeks old. The muscles of the hip and thigh were not differentiated from each other or their tendons, and consisted of pale homogeneous tissue. The gross proportions and relations of the capsule, femoral head and acetabulum were similar to those of the fetus at term and to the adult hip joint. The femoral head was smoothly rounded and hemispherical and fitted snugly into the well-formed acetabulum, where it was firmly held by a well-developed capsule. The femoral head and the acetabulum consisted entirely of cartilage, and measured 2 mm. in diameter. The femoral shaft was ossified through a length of 7 mm., and the iliac wing contained an ossification center 2.5 mm. across. The anteversion or anterior torsion (the angle between the longitudinal axis of the femoral head and neck and the transverse axis of the femoral condyles) was 15 degrees. The angle between the axis of the head and neck and the longitudinal axis of the shaft averaged 140 degrees. The motions of the joint, except extension which was moderately limited, closely approximated

those of the hips of young children. Thus, the hip joint may be considered perfectly formed in the embryo of ten weeks.

Seven hips of fetuses in the third, fourth, fifth and six months of life were seen, the femur varying in length between 3.3 and 8 cm. (Fig. 1 A, B). The muscles of these specimens were differentiated from each other almost completely and were easily identified, although they did not yet appear grossly to consist of muscle tissue and were poorly differentiated from their tendons. The blood vessels and nerves were easily distinguished. The gross proportions and relations of the structures at the hip were similar to those at term. The femoral head and the acetabulum consisted entirely of cartilage but ossification of the iliac wing had progressed to occupy one-half to two-thirds of its area and a large ossification center had formed in the ischium. There was a cartilaginous lip along the postero-superior half of the margin of the acetabulum, comparable to the bony lip of the adult, and the labrum glendoidale had formed. The femoral head varied in diameter between 0.4 and 1.4 cm. The femoral shaft was still slightly flexible. The ligamentum teres was well formed but could be torn with little force. The ante-version of the femoral neck was 20 to 25 degrees, and the inclination of the neck to the shaft 120 to 140 degrees. The motions of the joint were complete except extension, which was limited to about 145 degrees by the twisting of the capsule. The fibers of the capsule were seen to run parallel to the neck with the hip flexed to 90 degrees, and, upon extension, to tighten by torsion, resulting in this limitation.

Eight hips of fetuses in the seventh and ninth months were examined, the femora varying between 9 and 10.5 cm. in length. (Fig. 1 A, B.) The muscles were well differentiated and their tendons could be distinguished. Blood vessels and nerves were well developed. The ossified portion of the innominate bones occupied about five-sixths of the mass of each, but the acetabulum and femoral head were entirely cartilaginous. The anterior-inferior quadrant of the aceta-

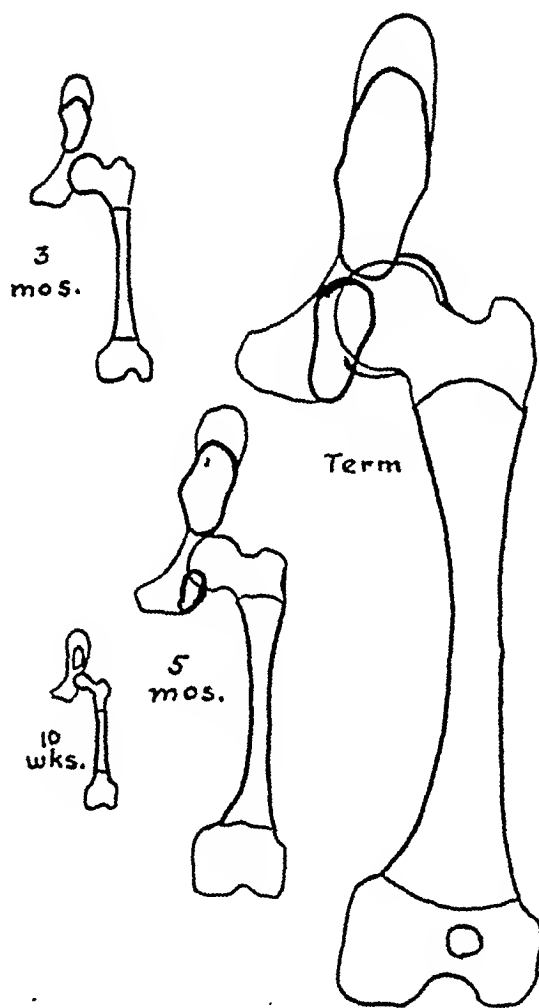


FIG. 1.—(A) Fetal specimens ($\frac{1}{2}$ actual size) at ten weeks, three months, five months, and term, showing size and shape of femur and innominate bone, with amount of ossification. Gross appearance similar to adult. Femoral head and neck and acetabulum are well-formed in cartilage, capsule and ligamentum teres well-developed.

bulum was shallow and the cartilage thin. The labrum glenoidale and the acetabular rim were well developed. The femoral head was 1.6 to 2.0 cm. in diameter. The ligamentum teres was 5 mm. in cross section and, in one instance, traction of several pounds was applied and a plug of cartilage to which it was attached pulled out of the femoral head but the ligament did not rupture. The Haversian gland was well developed. Anteversion varied between 20 and 40 degrees, and the inclination of the neck on the shaft was 110 to 120 degrees. Extension was limited to 160 degrees. The limitation of exten-



FIG. 1.—(B) Roentgenograms of fetal specimen at three months and at five months (actual size) and at term (reduced $\frac{1}{2}$).

sion by the twisting of the capsule is considered to represent a phase in the evolution of the joint. (Fig. 2 A, B.) Young infants are found to have flexion deformities of the hips, gradually disappearing as the infants begin to stand. The hips of an infant of one year were studied also, but there were no additional findings of consequence.

The cause of congenital dislocation of the hip was not determined from this study. It was hoped that a clue could be obtained as to whether or not these dislocations are due to an hereditary defect, to a local metabolic disturbance or to the application of some force to the femur from uterine pressure or malposition *in utero*, but no defective hip was found, and no conclusion can be drawn here. It is likely that if the deformity is intrinsic to the development of the embryo it occurs in the anlage of the hip, as the joint is so well formed at and beyond the tenth week. There were differences in the male and female pelves of this group, comparable to those of adults, but none which would account for the great preponderance of congenital dislocation in female infants.

CONGENITAL DISLOCATION OF HIP

Should the deformity be the effect of the application of an abnormal leverage to the femur *in utero* it would appear that associated bowing of the flexible femur might follow such a force, but deformities of the femur are not found in

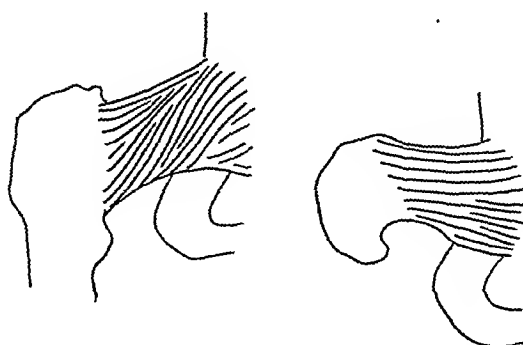


FIG. 2-A

2-B

FIG. 2.—(A) Hip joint capsule showing spiral twist of fibers in extension (from Spalteholz).

(B) These fibers are not twisted in the position of midflexion, but run nearly parallel with the neck.

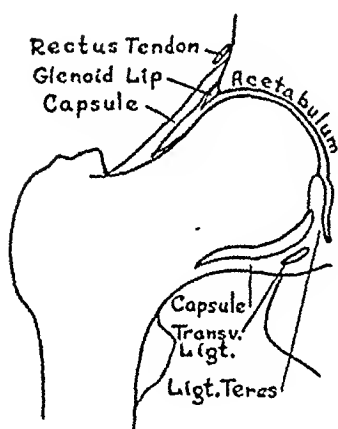


FIG. 3

FIG. 3.—Normal hip, showing rectus tendon, capsule, labrum glenoidale, ligamentum teres, and transverse ligament.

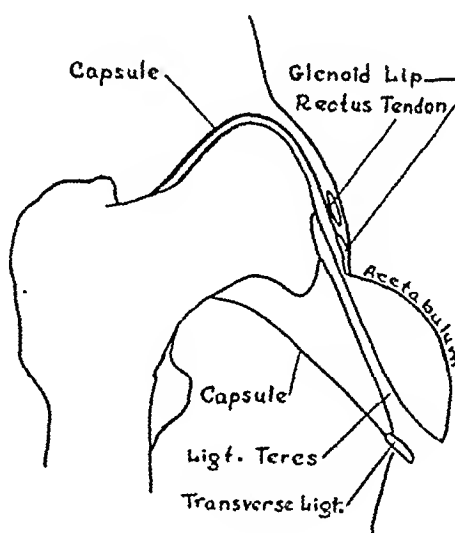


FIG. 4

FIG. 4.—Dislocated hip, showing outward and upward displacement of femur against ilium above acetabulum. Capsule and ligamentum teres elongated, capsule and transverse ligament pulled up over inferior portion of acetabulum. Labrum glenoidale and rectus tendon folded up against ilium. Acetabulum shallow, roof oblique, superior lateral margin defective. Femoral head flattened medially, protuberant inferiorly. Anteversion often present.

children with dislocated hips. No evidence has been found at birth or from operations upon young infants to support the possibility of dislocation by sudden trauma. It has been learned, through a personal communication from a research worker at the Rockefeller Institute, that congenital dislocation of

the hip occurs in rabbits, is apparently hereditary, and may be inbred. We have no evidence that the condition occurs in other animals, but an extensive search was not made.

Dislocation could be due primarily to a relaxed capsule or to a deformity of the acetabulum. At operation, the capsule has always been found elongated, necessarily, but the acetabulum is frequently too well formed to justify the supposition that it is the only primary factor. The ligamentum teres is not normally taut in the ordinary positions, so its relaxation could not be the cause of congenital dislocation. It does not appear that anteversion of the femur is the cause of dislocation, and it certainly is not the sole cause, as many dislocated hips have been found without abnormal anteversion. The position of flexion, external rotation and adduction would favor dislocation, and anteversion would increase this tendency. It appears that the inception of the deformity probably occurs in early embryonic life, and it is likely that relaxation of the capsule is the primary factor. It is desirable that hips younger than the tenth week be carefully studied and that a thorough search be made by pathologists, obstetricians and gynecologists for dislocations of the hip in fetal specimens in order that the cause of this condition may be determined.

There are special anatomic considerations related to these early specimens which are of great importance in the treatment of congenital dislocation of the hip. The greatest relaxation of the capsule is in the midflexed position; thus, the opening into the acetabulum should be largest with the hip flexed, and with a constricted capsule reduction should be more likely in some flexion than in extension. (Fig. 2 A, B.) Furthermore, the immobilization of the hip in forced extension and internal rotation is likely to result in a temporary ischemia by the torsion of the capsule and may be followed by coxa plana. When the acetabulum is too small to receive the whole femoral head it is desirable to enlarge it; in the infant there is a thick mass of cartilage in the superior acetabulum, a moderate portion of which can be removed with a gouge without exposing the ossified portion of the bones, but in the older child bone would be exposed at a depth of about one-eighth inch. The cartilage of the inferior acetabulum is thin and incomplete in the infant; thus, gouging of this area would probably result in opening into the upper thigh or the pelvis. Finally, because the acetabulum is cartilaginous it is difficult in the stabilization operation to construct a bony shelf which would be low enough to really support the hip.

PATHOLOGY

More than 100 hips have been examined at operation by the author, he being the responsible surgeon for 60 of the hips. The operative records of 85 additional hips have been reviewed. These studies form the basis for the following observations:

The femoral head in almost all instances was dislocated outward, upward, and forward, the capsule and rectus tendon being elongated to follow the head (Figs. 3, 4, 5 and 6). The capsule was usually somewhat thickened. The

muscles, tendons and fasciae attached to the trochanters and their neighborhood, and the innominate bone, were elongated or contracted to fit the altered mechanical situation. Abduction was limited by the leverage of the femur against the ilium, with the adductor muscles resisting. The posterior dislocations were few and almost uniformly occurred in older children.

It seems likely that the posterior dislocation is simply the ultimate result of the primary anterosuperior dislocations in which the capsule becomes greatly elongated, allowing the head to rise upward and swing backward on the ilium, since it is limited anteriorly by the tendons attached to the spines of the ilium. The greater proportion of posterior dislocations reported by others may be due to the greater percentage of older cases. It is probable that a posterior dislo-

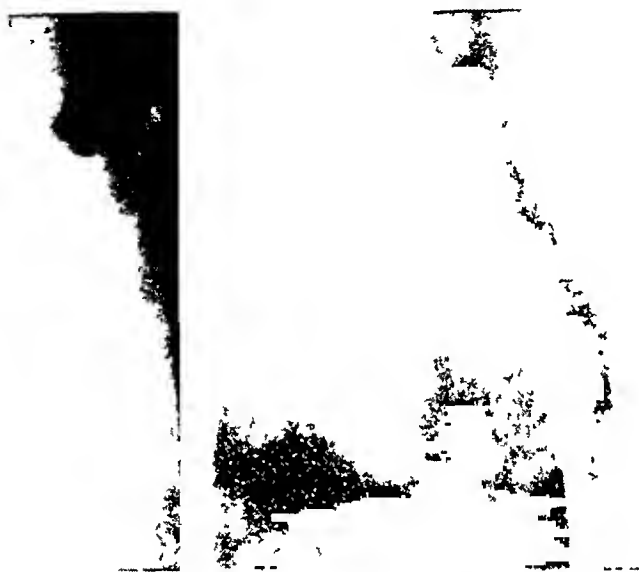


FIG 5.—Roentgenogram of bilateral dislocation in specimen at 8th fetal month, showing clearly the lateral and upward displacement of the femur.

cation is more likely to occur in the absence of marked anteversion, which throws the head forward, and this is borne out by the fact that anteversion in these posterior dislocations was usually absent, whereas there was often a retroversion.

Telescoping (instability on pushing up and pulling down the leg) was present in varying degree, being less marked in the anterior dislocations and often as much as one inch in the posterior ones (Figs. 4 and 6). There was rarely appreciable relaxation on pulling the femur laterally or backward and forward in the anterior dislocations, but such relaxation was usually present with a posterior dislocation, being sometimes as much as one-half inch. Several of the hips were not completely dislocated, a portion of the femoral head remaining under the superior lip of the acetabulum, the head sliding in and out on manipulation.

The principal obstructions to bringing the femoral head down to the level of the acetabulum, which is necessary for the accomplishment of reduction, were the adherence of the capsule to the ilium above the acetabulum and the

contraction of fasciae and muscle sheaths (Fig. 4). While the capsule was not always pulled up enough to result in adherence to the ilium, in the remaining cases the cartilaginous superior margin of the acetabulum, the labrum glenoidale and the rectus tendon were turned upward and deformed in such a way as to produce the same effect. The adductor longus and gracilis are the muscles which most commonly interfere with traction, the rectus femoris, sartorius,

FIG 6-A



FIG. 6-B

FIG. 6.—Roentgenogram of dislocated right hip as shown by displacement of femur laterally and upward. Telescoping, as shown by:
(A) Upward pressure—further displacement upward.
(B) Traction—femur down to nearly normal level in relation to acetabulum, in position for reduction.

tensor fascia femoris, iliopsoas, and gluteals being frequently contracted also. The fascia lata, particularly the iliotibial band, often offers strong resistance. The remaining adductors and the hamstrings rarely offer difficulty.

It was possible in many of the younger cases to bring the femoral head down to the level of the acetabulum by traction or flexion. In many such

instances an attempt was made to reduce the dislocation at open operation just before opening the capsule. It was found impossible in about half of these hips to accomplish the reduction, whereas about half of those reduced were found to redislocate easily upon bringing the thigh from the abducted position toward neutral. Upon opening the capsules the reasons for this difficulty were obvious.

The inferior portion of capsule was nearly always pulled up over the lower portion of the acetabulum and, in the children who had passed infancy, had become firmly attached to the margins of the acetabulum (Fig. 4). There was often also a slight side to side constriction of the capsule but in all hips up to



FIG. 6-C

FIG. 6.—(C) Result at age seven years, following failure of closed reduction at two months, successful open reduction at one year.

the age of six years, and in many of the older ones, the superior portion of the acetabulum was open and the superior portion of the capsule pulled upward away from the acetabulum. Thus, the deformity in the capsule is not a typical hour-glass contracture as so often described in the literature. Usually the transverse ligament of the acetabulum was pulled up with the capsule and hypertrophied, more effectively blocking the acetabular opening. Adhesions between the two synovial surfaces were rarely found. The Haversian gland, located in the acetabular fossa, hypertrophies in response to the absence of the pressure of the head. This hypertrophied gland was usually found to fill the inferior third of the socket. In some instances this tissue filled the whole acetabulum and gradually grew into and replaced the acetabular cartilage. In such hips the acetabulum was sometimes found to be obliterated by a mass of fibrous tissue. The ligamentum teres was elongated directly in proportion to the amount of dislocation. Often it maintained its usual diameters or became thickened, but in other hips it was greatly attenuated, split longitudinally, frayed, ruptured or absent. Some of the instances of ruptured or absent teres ligaments might have been due to the traumatism of closed manipulations, but

such conditions have been found in hips which were never manipulated. One or both stumps were usually found, except in the patients older than ten years. Occasionally the ligamentum teres presented evidence of recent injury. It usually oozed blood slightly from its proximal stump when divided at operation, but was only once seen to bleed enough to suggest that it was furnishing an important portion of the blood supply to the head.

The acetabulum was usually well formed in these infants, although in many hips the superior cartilaginous margin had been pushed up or even folded back upon the ilium, resulting in an oblique defective socket for the femoral head and a poor false acetabulum at the acetabular margin. Fig. 4. It appeared that the plastic cartilage had been molded by the pressure of the femoral head. If the capsule was sufficiently relaxed to permit complete dislocation upward on the ilium, the acetabular margin often escaped this deformity. In such cases the capsule was sometimes adherent to the ilium and cartilaginous in this area, forming a false acetabulum; in others the capsule was loose and movable and the femoral head had no fixed support. The depth of the acetabulum was not great enough to accommodate the head in about half of the hips, and in a smaller proportion the diameter of the head was greater than that of the acetabulum, whereupon the head could not be forced into it. These abnormalities were more frequent and more severe in older patients, the superior lip usually being absent.

The femoral head was frequently flattened medially; this was more common in the hips in which the head was impinging against the superior margin of the acetabulum. Near the junction of the head and neck inferiorly there was usually an enlargement of the bone, which was apparently due to the medial flattening of the head and probably associated with some circulatory disturbance. This elevation was frequently large enough to give the inferior half of the head a shape somewhat similar to that of a door knob. The femoral head and neck were often broadened. Occasionally there was some irregularity of the surface of the head in the older subjects.

TREATMENT

The ideal treatment of congenital dislocation of the hip is to secure the earliest possible reduction with the least possible traumatism, and with immobilization just long enough to result in permanent maintenance of the reduction. Such treatment should involve the least risk to the life of the patient from the anesthetic and from shock, and a minimal risk of infection. Simple open or closed reduction with immobilization would be insufficient to maintain the reduction of some hips because of the deformity of the femoral head or the acetabulum or the relaxation of the capsule, whereupon it is often necessary to correct these abnormalities to secure a good result. In other cases it is impossible to reduce the dislocation without unreasonable traumatism or division of tissues, followed by stiffness or weakness. The best alternative in such cases is the construction of a bony support for the femoral head in the dislocated position. The following statements in regard to treatment are based upon a

study of more than 100 closed and about 200 open operations and 50 shelf-stabilization operations, including follow-up examinations one or more years after operation, with particular reference to pain, fatigue, disability, limp, limitation of motion, telescoping and roentgenographic appearance.

It was found that forceful manipulations, even if successful in reducing the dislocations, often resulted in stiff hips and occasionally were complicated by such accidents as a fracture of the femoral neck. Subsequent open operations usually demonstrated that manipulative reduction was obviously impossible in most of the hips which were not reduced by manipulation (about 50 per cent). One-third of the dislocations which were apparently reduced recurred partially or completely. Accordingly, open operations gradually replaced closed operations in the older children, as they could be done with equal safety to the child, with less traumatism and with a greater chance of initial and final success. Obstructions to reduction, faulty acetabula and relaxed capsules could be corrected at open operation.

CLOSED REDUCTION

A closed reduction is the operation of choice in infants younger than one year. The hip can often be reduced under anesthesia by the simple maneuver of Hibbs: Flexion to 90 degrees, followed by abduction and extension, with manual lifting of the greater trochanter forward and sufficient internal rotation to counterbalance the anteversion present. It is unnecessary to use even the mechanical table with gentle leverage which Hibbs devised for the purpose, while such traumatizing procedures as that of Lorenz should be definitely avoided. Sometimes reduction can be accomplished by simple traction, internal rotation and abduction, but this is not the most favorable method as the capsule is twisted and narrowed upon extension. The hip should be immobilized after reduction in a plaster-of-paris spica in moderate abduction, and enough internal rotation to compensate for the anteversion, but the position should not be forced as the tension on the capsule may cause a circulatory disturbance which may result in coxa plana. The reduction should be verified by a roentgenogram; it is desirable to have the axis of the femoral head and neck directed toward or just below the center of the acetabulum. If a careful first attempt fails it is rarely possible to reduce the hip at subsequent attempts. The immobilization should be maintained for three to six months, varying with the stability of reduction. The child may be allowed to walk within two months of reduction. Weight-bearing is an aid to the proper molding of the joint surfaces if there is no tendency to subluxation.

There is a fair chance of success with a closed manipulation in children between one and three years old. Accordingly, at this age a single gentle manipulation may be attempted first when it is not obvious that such a procedure would be hopeless. The chance of failure with manipulation becomes progressively greater with increasing age after three years, so that in the hands of a surgeon familiar with the open operation it is undesirable to subject the child to a procedure which offers little probability of success except in an

occasional carefully selected case. However, when the surgeon is not familiar with the open operation, and it is not available in his locality, a closed manipulation is warranted at any age when there is a possibility of success. Adductor longus and gracilis tenotomies at the groin are often necessary in the older children and are far superior to the brutal methods of tearing these muscles, popularized by some of the earlier workers. Preliminary traction with adhesive tape or a Kirschner wire with such an apparatus as that of Thornton or the Taylor hip splint is often desirable, but it will usually require several weeks to secure a stretching which will permit reduction without great tension. Roentgenograms taken during traction will indicate the probability of bringing the head down to the level of the acetabulum (Fig. 6 A, B). The roentgenogram at this age will also demonstrate the obliquity of the acetabular roof, and a comparison of views taken standing and under traction will show the amount of relaxation of the capsule but will offer no clue to the width of the opening into the acetabulum.

OPEN REDUCTION

Open reduction of the hip should be attempted (in capable hands) after the age of one year whenever closed reduction fails, and should be the operation of choice in children past three years except in unusual instances. Open reduction should rarely be attempted in infants younger than one year because of the immaturity of the acetabulum, the additional operative risks of the anesthetic and infection by fecal contamination, and possible feeding complications. Operation should not, however, be delayed after this time because the deforming effect of weight-bearing begins to act as soon as the child begins to stand, months before he can walk alone. Reduction may be obviously impossible in children past eight years because of the absence of a socket or the extent of the dislocation as indicated by the standing and traction roentgenograms, but the possibility of reduction is often indeterminate at this age period and can only be decided at operation. As a shelf-stabilization operation is usually a desirable alternative, operation is justifiable even when reduction appears unlikely. Preliminary skeletal traction may be used if the femoral head remains high above the acetabulum in the roentgenogram made under traction.

The hip-joint is approached through the Smith-Petersen incision, care being taken to avoid injury to the vessels and nerves passing across the thigh just below the femoral neck, and the capsule is freed from the gluteus minimus above and the iliopsoas below. The capsule is incised anteriorly close to and parallel with the acetabulum and the joint explored. All procedures are performed with the utmost gentleness. Frequently the entrance to the acetabulum is not more than one-half of an inch in diameter and reduction is impossible without enlarging the opening. This is done by incising the capsule and transverse ligament inferiorly across the constriction. The capsule should never be cut superiorly, as its support may be lost and the cartilaginous lip of the acetabulum and the labrum glenoidale damaged. The femoral head may now be brought into the acetabulum by traction, abduction and internal rotation

or by the maneuver used in closed reduction. Usually it is found that the head cannot be entirely reduced because of the large mass of the redundant ligamentum teres and the enlarged haversian gland. The structures are therefore usually excised. The acetabulum may still be too small to hold the femoral head. The acetabular roof may then be enlarged and rounded by gouging the cartilage if it is sufficiently thick to allow this without exposing bone. When it has been necessary to gouge a new socket out of bone the hip almost always has become moderately stiff. Possibly this outcome could be avoided if the new socket were made sufficiently large and lined with fascia and the reduction maintained without tension, but this has not been done. Hey-Groves and Colonna report good results with freeing of the entire capsule medially and inserting it with the head into the acetabulum. The results with the shelf-operation have been so much better, particularly in the bilateral cases, than those in which a large area of bone was exposed in the acetabulum that the former is preferred. Occasionally the overgrowth of the cartilage of the head inferiorly is so great that reduction is obstructed. Some of this mass of cartilage may be trimmed away without stiffness resulting if bone is not exposed.

The capsule should be freed from the ilium superiorly when it is adherent. The rectus tendon, labrum glenoidale and superior cartilaginous lip of the acetabulum should be freed when they are everted, and allowed to come down to their normal levels. It is often impossible to bring the femoral head down to the level of the acetabulum without dividing some of the extrinsic resisting structures. An adductor tenotomy should be done first. It may be necessary to lengthen the rectus and sartorius tendons and the iliotibial band. The use of skids or forceful maneuvers for reduction is undesirable and unnecessary if the capsule and contracted structures have been properly released, or if preliminary traction is used. If it appears that the hip could not be reduced after lengthening these structures the possibility of reduction without great danger to nerves and the circulation of the joint and the extremity, and subsequent stiffness, is not sufficient to justify further procedures, particularly in view of the lack of such disability in older patients who have had no treatment whatever, and the favorable results of the shelf-operation.

When reduction is secured it is desirable to insure its maintenance. Frequently a large pocket remains in the capsule into which the head can easily redislocate, and usually the capsule will not contract sufficiently to obliterate this pocket. The relaxation is generally greater anterosuperiorly, due to the dislocation of the head in this direction. A crescent of this portion of the capsule is excised, large enough to correct the relaxation but not large enough to impair external rotation (Figs. 7 and 8).

The amount of anteversion and its effect are determined at operation. The hip is adducted with upward pressure with the knee forward, and again with the knee in sufficient internal rotation to correct the anteversion, and the angle of redislocation noted. If the femur dislocates as the abduction is reduced before reaching a neutral lateral position with the knee forward but remains

socketed to at least 20 degrees of adduction in internal rotation, it will usually be desirable to correct the anteversion. This is done three to six weeks after reduction by a transverse supracondylar osteotomy, the upper fragment being



FIG. 7

FIG. 7.—(A) Subluxation left hip; closed reduction failed; open reduction at age nine months.

(B) Same hip at age two years. Acetabulum oblique, head displaced upward in acetabulum and slightly laterally. Degenerative changes in head due to circulatory disturbance (coxa plana).

(C) Same hip at age six. Acetabulum deep and round, coxa plana healed.

maintained in internal rotation by a steel pin driven through the femur below the greater trochanter and incorporated in the plaster. A Kirschner wire may be passed through the femoral condyles for control of the lower fragment (Figs.

9 A, B, C). The anteversion need rarely be corrected unless it is greater than 45 degrees.

The hip is immobilized in a plaster of paris spica from midthorax to toes, including the opposite thigh if it is advisable to fully immobilize the pelvis. The hip should not be held under tension in plaster, so that coxa plana may be avoided. The spica may be removed in six weeks if the reduction is very stable, but usually is left on for two months, rarely longer. When there is a probability



FIG. 8.—Dislocation left hip at age nine following open reduction at age seven, with osteotomy for anteversion. Acetabulum elongated and very shallow; head deformed, and dislocated opposite upper margin of acetabulum; coxa valga. A shelf operation should have been done.

of stiffness the plaster may be bivalved from the foot to the groin three or four weeks after operation and daily motion begun. The child is not allowed to walk at once upon removal of the spica but is kept in bed for one to four weeks, and massage and motion begun. Roentgenograms are made with traction and with upward push to demonstrate possible instability. When pain and spasm are absent, motion is fair or good, and there is no telescoping, walking is begun, first with crutches, then without support. The principles of treatment at this stage are to begin mobilization at the earliest safe moment and to delay weight-bearing until the extremity has recovered sufficient function.

SHELF STABILIZATION

It is usually impossible to secure a stable reduction with good motion in a congenital dislocation of the hip after the age of ten years. Some of the hips at this age are stable and symptomless in the dislocated position. Others are

painful and weak, moderate telescoping is demonstrated in standing and traction roentgenograms, and oblique views of the hip reveal the absence of any bony support. Sometimes in younger hips reduction is not obtained, or with the femur reduced the socket is so poor that the hip cannot be made stable by the methods previously described. In these types of cases it is desirable to support the hip by a bony shelf built above it to prevent instability and further dislocation. The hip may be pulled down by preliminary traction but it is

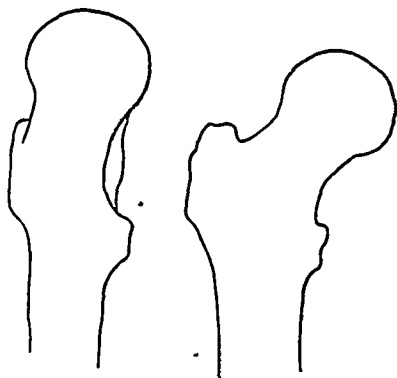


FIG. 9-A & B

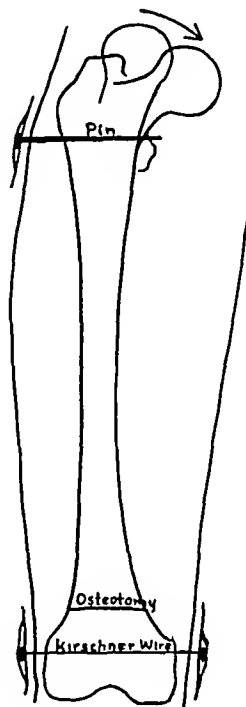


FIG. 9-C

FIG. 9.—Anteversion:

(A) Marked anteversion, favoring dislocation.

(B) Normal hip.

(C) Operation for correction of anteversion: supracondylar osteotomy, upper fragment held in internal rotation by pin through femur at level of trochanters, position of lower fragment may be maintained by Kirschner wire through condyles (outside joint capsule), both incorporated in plaster spica.

undesirable to leave it under any tension after the shelf is made, as such pressure often results in partial absorption and irregularity of the femoral head. The shelf may be turned down from the ilium, the acetabular roof may be turned down and wedged as advocated by Gill, or a shelf may be driven into a slot above the acetabulum (Figs. 11 A, B, C). The first type of operation has usually proven most satisfactory, and will be described (Figs. 12 A, B).

The hip is exposed as at open reduction except that most of the iliac wing is exposed subperiosteally, care being taken posteriorly to avoid injury to the gluteal vessels and nerves, and usually it is unnecessary to free the capsule

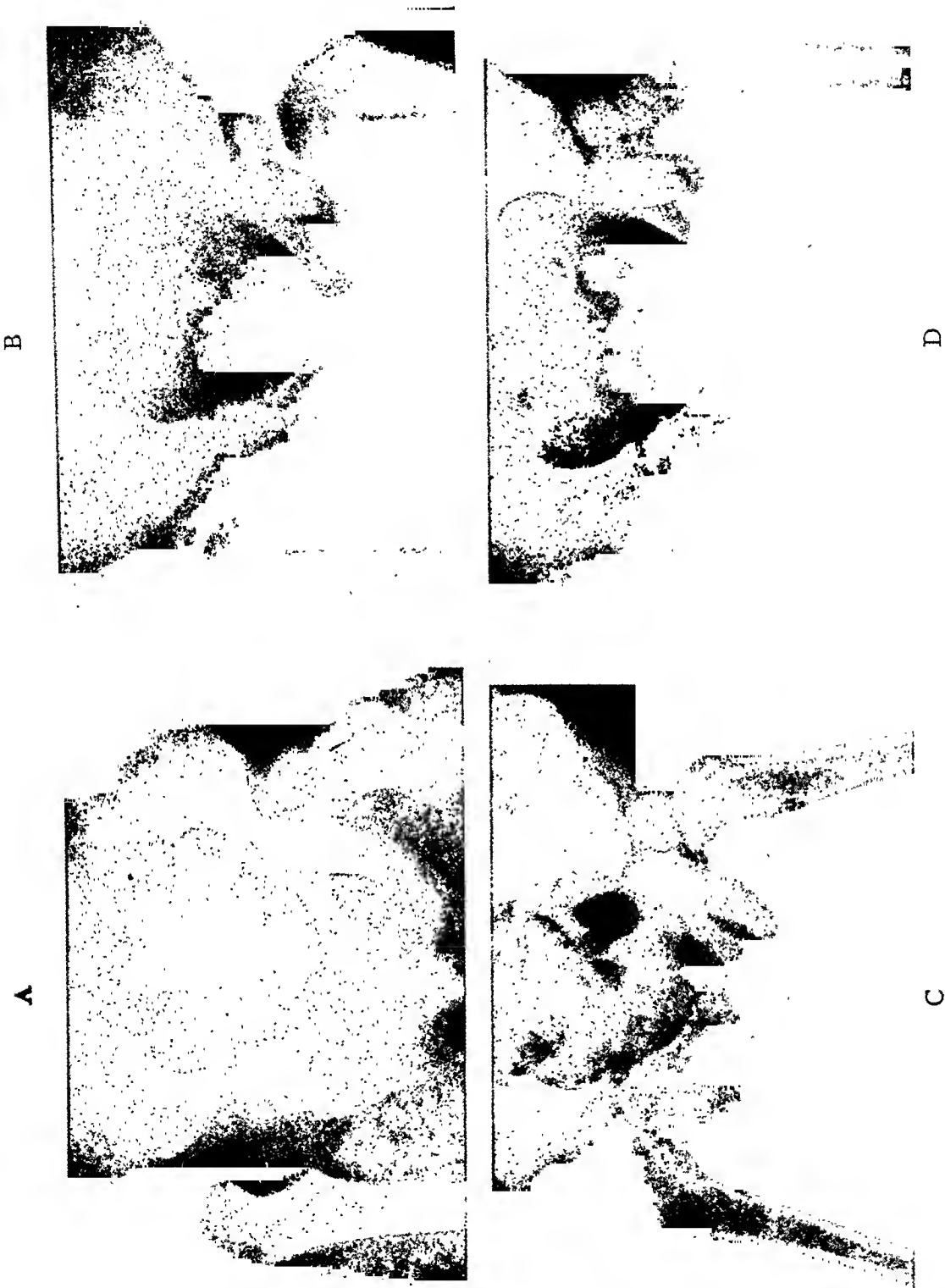
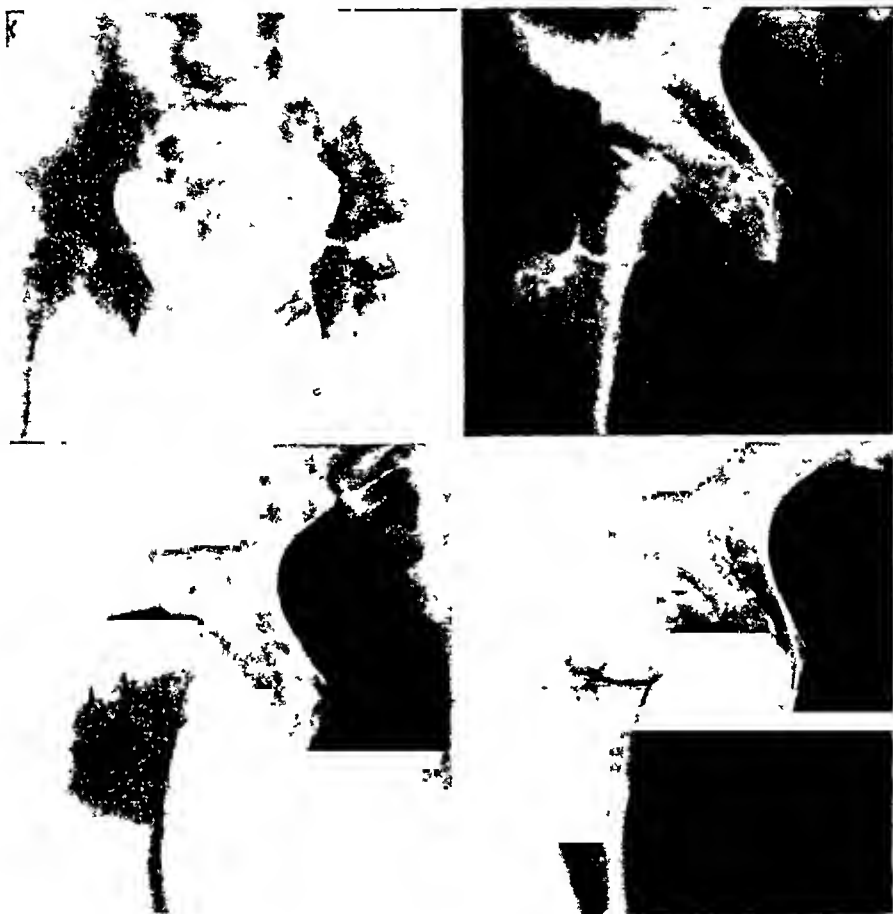


FIG. 10—(A) Dislocation right hip age two years; acetabulum shallow and oblique; marked anteversion. (B) Same in internal rotation to show correction of anteversion. (C) Same, three months after open reduction. (D) Same, age four, two years after reduction. Slight subluxation. Coxa plana.

inferiorly. Taut structures are divided or lengthened to release tension, as in the open reduction, unless the capsule is very lax as in the high posterior dislocations where any further release would result in risk of the head slipping from underneath the shelf. The capsule is not opened unless reduction is to be attempted. Lateral and anteroposterior relaxation are tested to determine the width and length of shelf necessary. The shelf should be large enough to cover

10-E

10-F



10-G

10-H

(E) Same, age seven; further subluxation. Coxa plana healed.

(F) Same, age fourteen, further subluxation; acetabulum elongated and shallow. Head deformed.

(G) Shelf operation at age sixteen; iliac slab driven into slot above acetabulum.

(H) Same, one year after shelf operation. Relief of pain; improvement in gait and strength of hip.

the crest of the head in any position which it can assume. The proposed shelf is marked on the ilium in the form of a broad inverted U. A slab of bone, large enough to brace the shelf, is cut from the lateral cortex of the iliac wing anterosuperiorly and smaller reinforcing slabs and large chips are cut from the

CONGENITAL DISLOCATION OF HIP

remaining available portion of the ilium in such a manner as to weaken the ilium as little as possible. The shelf is freed with curved osteotomes to its base, usually three-sixteenths to one-quarter inch thick, and turned down over the capsule and femoral head, where it is blocked by a large slab wedged between the lateral margin of the shelf and the upper margin of its bed at an angle of about 45 degrees to the ilium. Reinforcing slabs and chips are inserted to fill the gaps, and particular care is taken to have the shelf perpendicular to the extended thigh. When the hip has been reduced or is merely subluxated the shelf includes a portion, if not all, of the false acetabulum and, occasionally, the

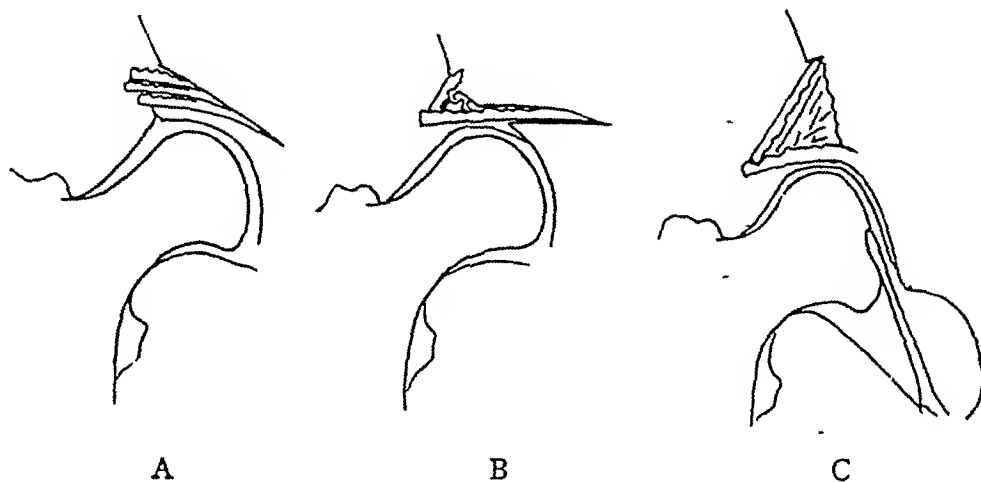


FIG. 11

FIG. 11.—Shelf stabilization operation: -

(A) Hip reduced, roof of acetabulum turned down and wedged down by bone slabs cut from wing of ilium. For young children.

(B) Hip reduced, slab from iliac wing driven into slot at superior margin of acetabulum, and reinforced by block and chips above. For older children.

(C) Hip not reduced. Shelf turned down from wing of ilium and blocked there by slabs and chips from iliac wing. For older children and adults.

oblique portion of the acetabulum proper. The shelf does not become detached if handled carefully, additional support being furnished by the soft tissues at its base. Occasionally it is desirable to suture the slab to the shelf to prevent its slipping. The muscles are lifted forward over the shelf and carefully sutured to the tissues at the anterior inferior spine, the wound is sutured anatomically, as for open reduction, and a snug double spica applied to include the lower thorax and the foot of the affected side. The spica is worn for eight to ten weeks and weight-bearing begun two to four weeks later. The principles of postoperative treatment are similar to those for open reductions except that the solidity of the shelf for supporting the body weight must be determined roentgenographically.

ARTHROPLASTY, FUSION, AND OSTEOTOMY

Occasionally open or closed reduction results in a hip that is painful and somewhat stiff and deformed. The usual deformity is flexion, adduction and

internal rotation. There is little chance for improvement of these hips with exercises after two years from the time of reduction, and manipulation is likely to do more harm than good. Arthroplasty with the vitallium cup has rarely been tried in such hips under the age of ten years, but we have had one very good result in a child of five, and one fair result at the age of six, and good

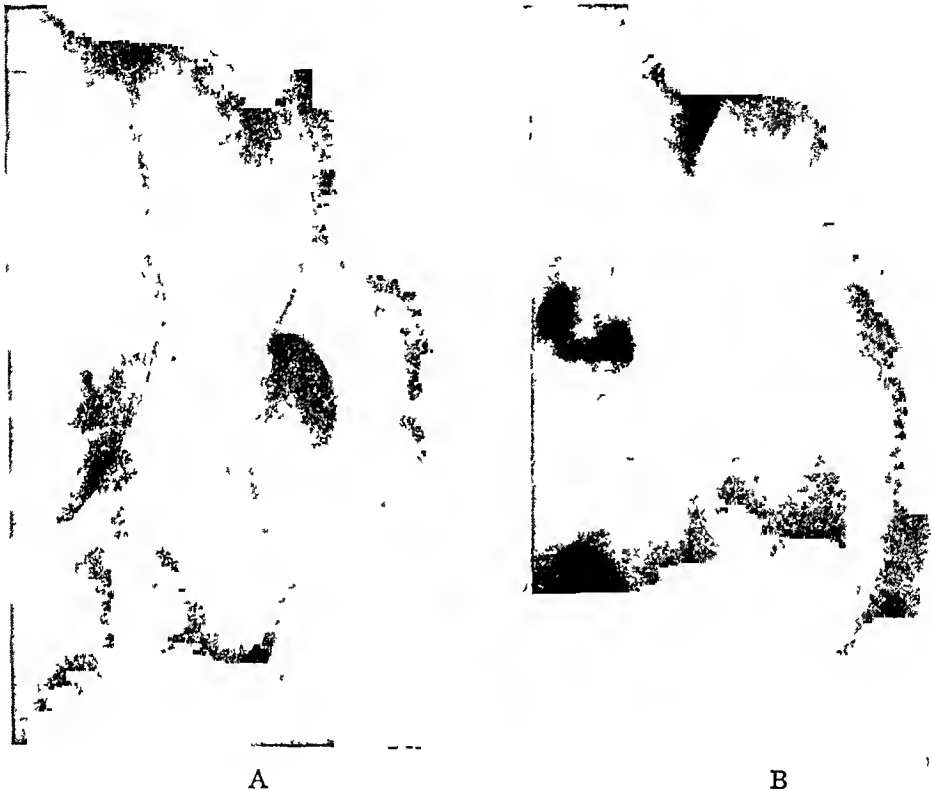


FIG 12

FIG. 12—(A) High dislocation of left hip with marked instability.
(B) Shelf turned down over head and reinforced with slabs and chips; one year after operation.

results in two adults. The cup was removed from the hip of the child of five after two years, and a well-formed head and acetabulum found. Arthroplasty is the operation of choice when both hips are affected, especially if both hips are stiff and deformed (Fig. 13). Hip fusion usually gives a better result if only one hip is affected, as there is no pain and the subject is able to stand, and even run, jump, dance and swim with the hip fused. We have performed only 13 hip fusions for congenital dislocation in the past 11 years, with almost uniformly good results. Both arthroplasty and fusion are difficult or impossible, however, if the hip is dislocated high on the ilium, as the iliac wing is so thin that there is not enough bone for either operation. A modified fusion may be done in such a case by using a tibial bone graft from the femur to the acetabulum or ischium through a subtrochanteric osteotomy. The Lorenz or the Schanz

CONGENITAL DISLOCATION OF HIP

osteotomy may be tried when both hips are dislocated high on the ilium, for relief of severe pain and instability.

CONCLUSIONS

The anatomy and development of the fetal hip from the tenth week to birth, the evolution of the anteversion and the torsion of the capsule, and the pathology of congenital dislocation of the hip as seen at operation from infancy to



FIG. 13.—Bilateral congenital dislocation of hips, untreated, with marked deformity of femoral heads, necks, and acetabulums, and osteo-arthritis with cystic degeneration. Marked pain and disability. Suitable only for vitallium cup arthroplasty.

adult life are described. Congenital dislocations of the hip should be reduced as soon as possible after they are recognized, as the results are more favorable in proportion to the early age of the patient. Closed reduction is the treatment of choice for infants if it can be accomplished with little traumatism. Open reduction should be used for infants older than eight months if closed manipulations fail and for all older children when there is any possibility of securing a movable stable hip. Important anatomic points and variations in procedure, advisable for securing the best result in the individual case, are stressed. When open reduction fails or is inadvisable, the shelf-stabilization operation, or the vitallium cup arthroplasty should be used in selected cases, or an arthrodesis done. The results of the surgical treatment of congenital dislocation of the hip are very favorable when there is careful selection of type of treatment, due regard for operative technic and atraumatism, and proper after-care.

REFERENCES

- ¹ Strayer, L. M.: The Embryology of the Human Hip Joint. *Yale J. Biol. & Med.*, 16, 13, 1943.
- ² Farrell, B. P., and Howorth, M. B.: Open Reduction in Congenital Dislocation of the Hip. *J. Bone & Joint Surg.*, 17, 35, 1935.
- ³ Howorth, M. B., and Smith, H. W.: Congenital Dislocation of Hip Treated by Open Operation: A Report of 70 Cases. *J. Bone & Joint Surg.*, 14, 299, 1932.
- ⁴ Ferguson, A. B., and Howorth, M. B.: Coxa Plana and Related Conditions at the Hip. *J. Bone & Joint Surg.*, 16, 781, 1934.
- ⁵ Howorth, M. B.: Shelf-stabilization of the Hip. A Report on 53 Cases: With Particular Emphasis on Congenital Dislocation. *J. Bone and Joint Surg.*, 17, 945, 1935.

AUTOGENOUS DICED CARTILAGE TRANSPLANTS TO BONE

AN EXPERIMENTAL STUDY

STUART D. GORDON, M.B., F.R.C.S.(C), M.S.(T), F.A.C.S.

AND

RUPERT F. WARREN, B.Sc., M.D.

TORONTO, CANADA

THIS INVESTIGATION was undertaken to study the histologic changes involved when diced autogenous rib cartilage was placed in a long bone defect. The immediate and late effects of such a transplant on shaft bone and the ultimate fate of the grafted tissues themselves were studied over a period of three months.

The literature on chondral grafts is extensive. It has been established that cartilage may be transplanted from one site to another in the same animal, and not only continue to survive but also to grow. Growth follows more readily if the new site is vascular. Cartilage may be grafted successfully from one animal to another of the same species and behave as an autogenous graft. This ability to survive homografting is shared by only one other tissue, namely, cornea. Cartilage is able to survive repeated transplantations and by successive regrafting will long outlive the normal lifespan of that particular animal. This tissue then possesses potential immortality. Survival in these cases is not due to regeneration from a viable perichondrium, as was once believed, but rather depends on the survival of individual chondrocytes themselves. (Dupertuis,¹ Loeb,²⁻⁷ Bisgard⁸).

Many uses have been made of both living and dead cartilage in plastic surgery (Pierce,⁹ Gillies,^{10, 14} Peer,¹¹ Placio Posse,¹² Adler,¹³ and others). One consistent objection to living cartilage grafts is their tendency to curl. Young¹⁵ deposited small pieces of autogenous cartilage over the rectus fascia in dogs. He concluded, "autogenous rib cartilage finely chopped and seeded over the rectus fascia in a dog stays viable and fuses together into a solid sheet of opaque-like material." This fusion is by fibrous tissue. Grossly this mass has some of the properties of fibro-elastic cartilage. Peer¹⁶ used this principle in humans and stored excess autogenous material in small pieces in the patients' soft tissues for later use in plastic repairs. He found the 'interdice' spaces filled with blood clot followed by an ingrowth of connective tissue and numerous blood vessels. "The smaller the graft, the better its chance of complete survival after transplantation." Practical use of diced cartilage has been made in restoring contours in plastic surgery (Young,¹⁷ Peer¹⁸).

There has been a considerable amount of experimental work done on cartilage but to date no one has investigated the tissue changes that occur when diced cartilage is transplanted to a fresh bone defect. Previous studies have been directed to the reactions in soft tissues, where blood supply is adequate.

It has already been mentioned that survival and growth are known to result. But will cartilage continue to grow in bone? Is it replaced by bone and does it stimulate osteogenesis?

Material and Method.—Since early ossification in canine costal cartilage has been noted by other workers (Young¹⁹), and confirmed here, the rabbit was selected as the experimental animal of choice.

Under general anesthesia a small portion of the anterior ends of the lowest two ribs were obtained. Microscopic sections proved this to be true cartilage. The material was immediately diced into small cubes about 1 mm. in diameter. These were deposited in a long bone defect of a forelimb of the same animal. This defect was obtained by means of a small rongeur which removed the cortex over an area of approximately 0.6 cm. by 0.8 cm. When bleeding had ceased the defect thus created was tightly packed with the diced costal cartilage. The incisions were closed in the usual manner.

Animals were sacrificed at 24 hours, and thereafter at weekly intervals up to three months. In all, some 18 animals were studied. Sections were taken of the decalcified bone in the longitudinal axis of the limb so as to include the cartilage graft lying between normal shaft bone on either side of the transplant. Sections were studied after staining with hematoxylin and eosin.

OBSERVATIONS

Twenty-four hours after operation diced cartilage is seen lying within the bone defect, surrounded by blood clot, serum and narrow débris. No evidence of osteogenesis is yet visible.

One week later islets of living cartilage are surrounded by an ingrowth of connective tissue cells, blended with the perichondrium and running parallel to the dice surfaces. New cancellous bone trabeculae are seen within the medullary cavity on either side of the artificially repaired defect.

At the end of two weeks central portions of some dices have begun to show cystic changes, with flattened chondrocytes lying against one side of their enlarged lacunar wall. Towards the periphery of each dice, there is normal appearing matrix and cellular structure. Cancellous bone has continued to encroach around the dices and there is a distinct demarkation between perichondrium and the surrounding connective tissue cells.

In about two and one-half to three weeks it is evident that not only is the dice surviving but the matrix of new cancellous bone has become structurally continuous with the matrix of the cartilage. This is not a matter of new bone being laid down in an area where the dice has been absorbed, for in the majority of cases the dice surface is not exposed, nor are tongues of invasion seen. Rather, it seems as though new bone had been laid down on the surface of the dice and the matrices had been fused together. In the following ten weeks the cartilage graft becomes progressively smaller. Nowhere is there evidence of absorption. No giant cells are seen and no inroads or tongues of connective tissue cells, except in those areas where necrotic or degenerating cartilage is found. Central portions of dices are made up of degenerating tissue, the

lacunae empty or greatly enlarged, while the surface of the dice is made up of normal healthy cartilage with a tendency for the cells to line up parallel to the surface of the dice.

At the end of three months a few small islets of cartilage persist deeply embedded in bone, but appearing healthy and having a mottled uneven line of demarkation where matrices of bone and cartilage meet.

DISCUSSION.—Cartilage survives when transplanted to bone as it does when placed in soft tissues. It is evident that some process of replacement by bone is present here, not seen when cartilage is grafted to nonosseous sites. Replacement is not accomplished after absorption as would be the case with a bone graft. Instead it seems to be a creeping replacement after the two matrices become continuous.

Cartilage cells more remote from nutrition tend to degenerate and the lacunae to enlarge. Tissue nearer the graft surfaces is not influenced to the same extent. This is reasonable in view of the strangling effect of new bone matrix surrounding the dice. The problem of finer dicing for better survival must have its limitations as each dice becomes isolated by new bone in three weeks.

When a bone defect is repaired by tightly packed cartilage there is the classical picture of repair following injury. Ham²⁰ states: "Pieces of dead bone, or even masses of powdered calcium salts, can be considered to possess the distinct ability to incite a foreign body type of response.

"On the other hand, calcium salts, dead bone or calcified cartilage also exert a second type of stimulus particularly towards osteogenic cells which tend to incite new bone formation." We believe that living autogenous cartilage dices incite this second stimulus also.

Replacement of cartilage by bone is logical. It conforms to the pattern of growth in the young animal and the repair of fractures in the injured. In the latter cartilage is often seen in callus formation. Accordingly, some may question the authenticity of small islets of cartilage persisting in older grafts, suggesting perhaps they are the products of reparative processes. The constancy of the occurrence, the uniformity of the histologic sequence points strongly to the grafted tissue as being responsible for such islets in most cases.

In lower animals considerable repair of a long bone defect is accomplished without any graft. The persistence of viable cartilage islets in the midst of such active growth of bone emphasizes again its remarkable powers of survival.

CONCLUSIONS

1. When diced autogenous costal cartilage is used to repair a long bone defect in the rabbit, it remains viable for three months.
2. Cartilage dices act as a framework for the deposition of bone in a defect.
3. Replacement of cartilage by bone is slow and is not always preceded by absorption but tends to follow a creeping replacement process with a continuity of the two matrices.

REFERENCES

- ¹ Dupertuis, S. M.: Actual Growth of Young Cartilage Transplants in Rabbits. *Arch. of Surg.*, **43**, 32-63, 1941.
- ² Loeb, L.: Autotransplantation and Homoio-transplantation of Cartilage and Bone in the Rat. *Am. J. Path.*, **2**, 315, 1926.
- ³ Loeb, L.: Syngenesiotransplantation in the Rat. *Am. J. Path.*, **3**, 45, 1927.
- ⁴ Loeb, L.: Syngenesiotransplantation in the Guinea-pig. *Am. J. Path.*, **3**, 29, 1927.
- ⁵ Loeb, L.: Autotransplantation and Homoio-transplantation of Cartilage in the Guinea-pig. *Am. J. Path.*, **2**, 111, 1926.
- ⁶ Loeb, L.: Transplantation and Potential Immortality of Mammalian Tissues. *J. Gen. Physiol.*, **8**, 417, 1926.
- ⁷ Loeb, L., and Siebert, W. J.: Transplantation of Skin and Cartilage in Chickens. *Arch. Path.*, **20**, 28, 1935.
- ⁸ Bisgard, J. D.: Experimental Studies of Reparative Costal Chondrogenesis and of Transplanted Bone. *Surg. Gynec. and Obst.*, **58**, 817, 1934.
- ⁹ Pierce, G. W.: Reconstruction of the External Ear. *Surg. Gynec. and Obst.*, **50**, 601, 1930.
- ¹⁰ Gillies, Sir H.: Reconstruction of the External Ear with Special Reference to the Use of Maternal Ear Cartilage as the Supporting Structure. *Revue de Chir., Struct. tive*, **7**, 169, 1937.
- ¹¹ Peer, L. A.: Types of Buried Grafts Used to Repair Deep Depressions in the Skull. *J. A. M. A.*, **115**, 357, August, 1940.
- ¹² Posse, R. Palacio: Utilization de la Ciba Osteocartilaginosa Para la Correccion de la Falta de Desarrollo del Menton. *Arg. de cir. clin. a Exper.*, **6**, 209-301, April-June, 1942.
- ¹³ Adler, D.: Cartilage Refrigerada. *Arg. de cir. clin. a Exper.*, **6**, 608-611, April-June, 1942.
- ¹⁴ Gillies, Sir H.: New Free Graft (of Skin and Ear Cartilage) Applied to Reconstruction of Nostril. *Brit. J. Surg.*, **30**, 305-307, 1943.
- ¹⁵ Young, F.: Autogenous Cartilage Grafts. *Surgery*, **10**, 7, 1941.
- ¹⁶ Peer, L.: Cartilage Grafting. *S. Clin. of N. A.*, **24**, 404, 1944.
- ¹⁷ Young, F.: Cast and Precast Cartilage Grafts. *Surgery*, **15**, 735, 1944.
- ¹⁸ Peer, L.: Diced Cartilage Grafts. *Arch Otolaryng.*, **38**, 156-165, 1943.
- ¹⁹ Young, F.: Homogenous Cartilage Grafts. *Surgery*, **17**, 616, 1945.
- ²⁰ Ham, A. W.: In Cowdry's "Special Cytology" 2nd Ed. Vol. II. P. 981-1051. Paul B. Hoeber, Inc., New York, 1932.

EXPERIMENTAL CARCINOMA OF THE GALLBLADDER*

SUPPLEMENTARY DATA

N. N. PETROV, M.D., AND N. A. KROTKINA, M.D.

LENINGRAD, U.S.S.R.

THE EXPERIMENTAL PRODUCTION of carcinoma of the gallbladder in animals was demonstrated by our work, published in 1933.¹ However, the results have not been accepted in the literature on this subject, partly due to our presentation of incomplete data. For example, in a review of the present status of the question in 1940, Lam² stated:

"Petrov and Krotkina reported, in 1928, that they could not reproduce carcinoma of the gallbladder in the guinea-pig by the introduction of foreign bodies, but in 1933 they reported success. Nineteen guinea-pigs were used. Small glass tubes containing one microgram of radium were inserted into the gallbladders of 12 animals, and seven controls had empty glass tubes inserted. They were trying to confirm the work of Barlow,³ who had presented evidence that cancer of the gallbladder was due to the radioactivity of gallstones. They reported that carcinoma developed in two animals in each group. Three of the animals were said to have had multiple metastases and died of cancer. The fourth was operated upon at the end of the experimental period, and a carcinoma of the common duct was found. However, these authors did not choose to publish photomicrographs of the tumor tissue, but submitted drawings instead. Hence, it can be stated that, at the present time, experimental proof that gallstones cause cancer is lacking."

For fuller review, it should be noted that our original experiment, published in 1928, was relatively short-term in character, and only four animals survived longer than 15 months. In the second investigation, published in 1933, the first malignant tumor was found 16.5 months following the experimental procedure. Furthermore, two animals of the second group had not only metastases but also complete destruction of the gallbladder by tumor; hemorrhages in the peritoneum of one animal and in the pleura of the other were also encountered. Photographs of both these animals were included in our article.¹

Absence of photomicrographs was undoubtedly a deficiency, especially since other authors reporting positive results on carcinogenesis in the gallbladder following introduction of foreign bodies,^{3, 4, 5} also, did not present evidence that was sufficiently objective. This defect regarding the work of Leitch⁵ had been criticized by Creighton,⁶ and Rouillard.⁷ We, therefore, desire to supplement our original report at this time. The delay in the answer to Lam's² criticism was occasioned by war conditions in Leningrad during 1941-1944. We referred to our collection of material on the original experiments and made histologic sections, as far as was possible, under the difficult circumstances.

* The manuscript for this article was received and translated by the American Review of Soviet Medicine, in New York City, N. Y.

The most illustrative material of all our positive results is hereby presented in the new photomicrographs.

In addition, we present photomicrographs from one new experiment in which 11 guinea pigs survived 14 to 34 months following the introduction into the gallbladder of glass rods, measuring 12 x 2.5 mm. The rods were sterilized by heat. In one animal there was considerable thickening of the gallbladder wall (to 3 mm.) 14 months following the experimental procedure. Atypical

FIG. 1

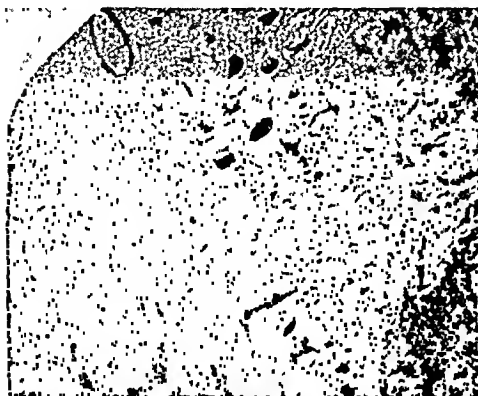


FIG. 2

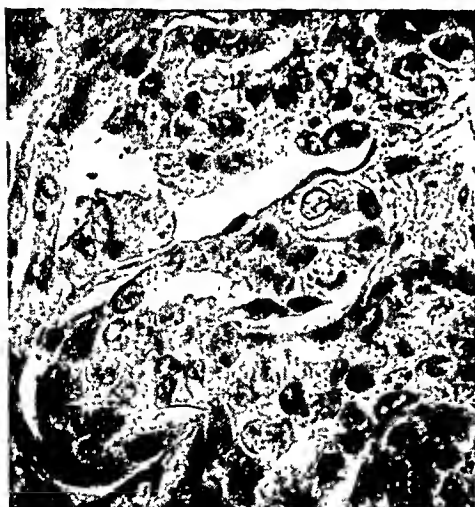
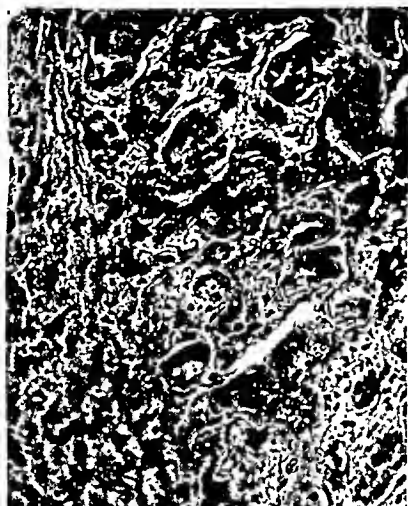


FIG. 3



FIG. 4

FIGS. 1-3.—No. 262: Growth of tumor in the liver. Low and higher magnifications.
FIG. 4.—No. 262: Metastasis in the lung.

epithelial cells, with hyperchromatic nuclei, grew in glandular patterns between muscle bundles of the gallbladder wall. A tumor mass, approximately 1 cm. in diameter, was found in the mediastinum between normal lungs. The mass was composed of glandular tissue similar to the original tumor, lying between fibrous connective tissue; in places the lumen contained amorphous material and leukocytes. This case was an early form of adenocarcinoma of the gallbladder, with metastasis to the mediastinum (Figs. 16-18).

In addition to the 11 guinea pigs mentioned above, we have three other

CARCINOMA OF GALLBLADDER

experiments, comprising 22 animals living from 15 to 40 months following the introduction of glass rods or tubes into the gallbladder. The animals did not develop malignant tumors, but, as in previous experiments, over half developed hyperplastic growth of the epithelium of the gallbladder.

In answer to doubts expressed up to the present concerning the production of malignant epithelial growth of the gallbladder by hard foreign bodies, *we present photomicrographs of all our positive observations.* Our experiments

FIG. 5

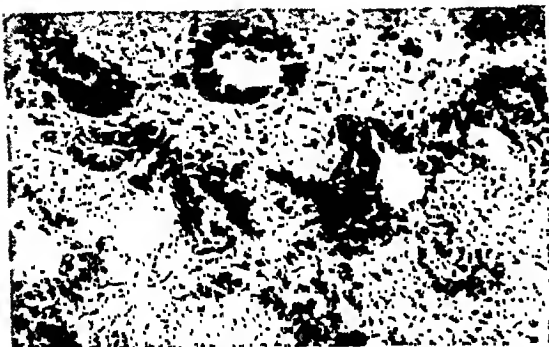


FIG. 6

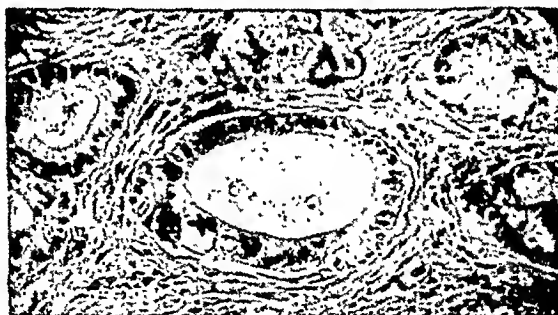
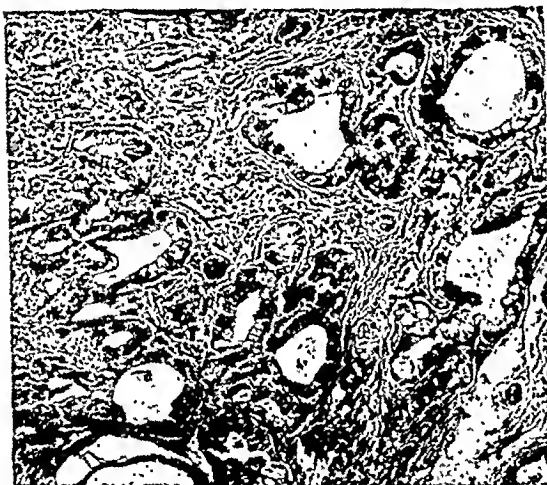


FIG. 7

FIG. 8

FIG. 5.—No. 262: Metastasis in the lung.

FIG. 6.—No. 267: Growth in the gallbladder wall.

FIGS. 7-8.—No. 267: Growth of tumor around common bile duct.

are summarized in Table I, which shows that five instances of malignant growth were obtained in 51 guinea-pigs following the introduction of hard foreign bodies into the gallbladder.

PROTOCOLS OF FIVE POSITIVE RESULTS

No. 262.—*Experiment 2:* Glass tube with radium. Tumor found 34.5 months after experimental procedure. Tumor penetrated diaphragm and destroyed the gallbladder. Metastases to lungs and omentum. The glass tube had disappeared. *Histologic Diagnosis:* Adenocarcinoma (Figs. 1-5).

No. 267.—*Experiment 2:* Glass tube with radium. Tumor found 39.5 months after experimental procedure. Tumor around common bile duct, penetrating into the liver. The glass tube had disappeared. *Histologic Diagnosis:* Adenocarcinoma (Figs. 6-8).

No. 270.—*Experiment 3*: Sterile glass tube. Tumor found 16.5 months after experimental procedure. Gallbladder destroyed, tumor penetrated liver. Metastases to lungs, diaphragm and omentum. Hemorrhagic ascites. *Histologic Diagnosis*: Adenocarcinoma (Figs. 9-12).

No. 294.—*Experiment 3*: Sterile glass tube. Tumor found 31.5 months after experimental procedure. Metastases to lungs, diaphragm, and omentum. Hemorrhage in pleural cavities. *Histologic Diagnosis*: Adenocarcinoma (Figs. 13-15).

FIG. 9

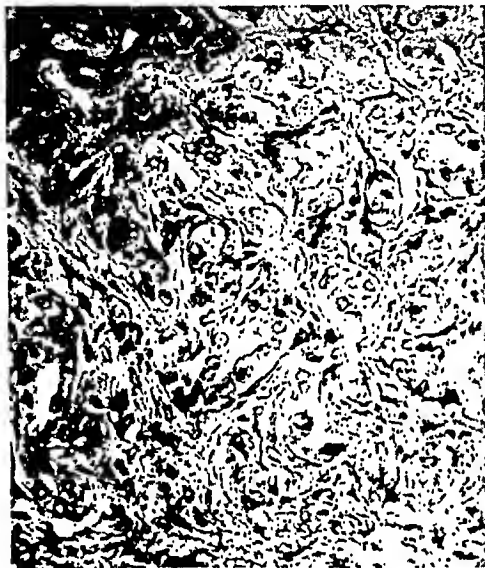


FIG. 10

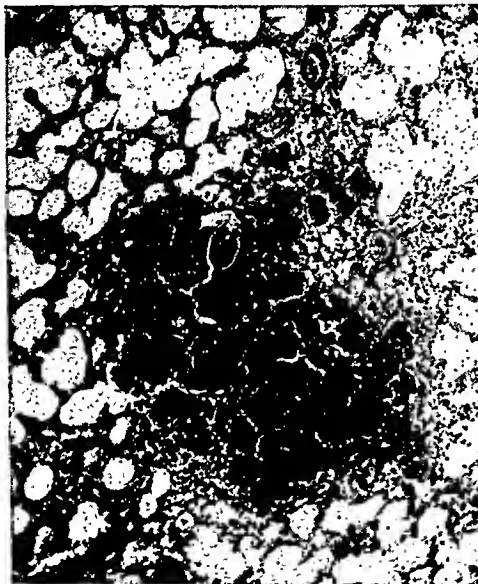
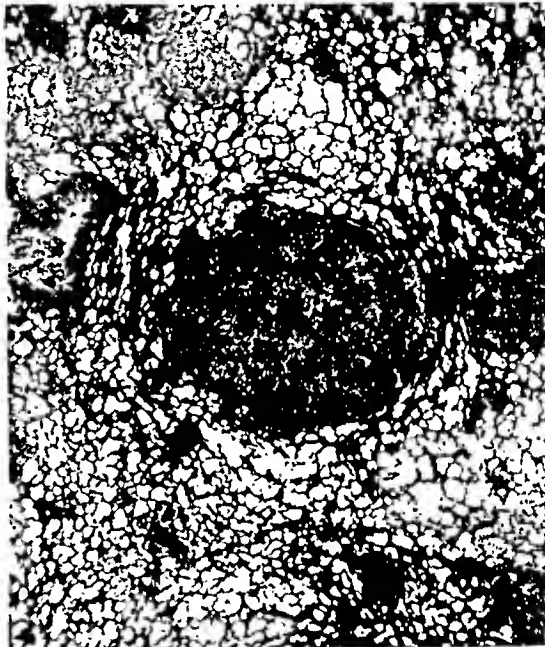


FIG. 11

FIG. 12

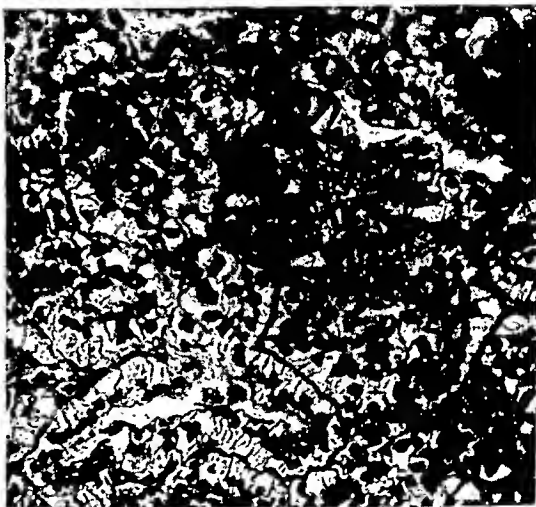


FIG. 9.—No. 270: Growth of tumor in the liver.

FIGS. 10-12.—No. 270: Multiple metastases in lungs.



FIG. 14

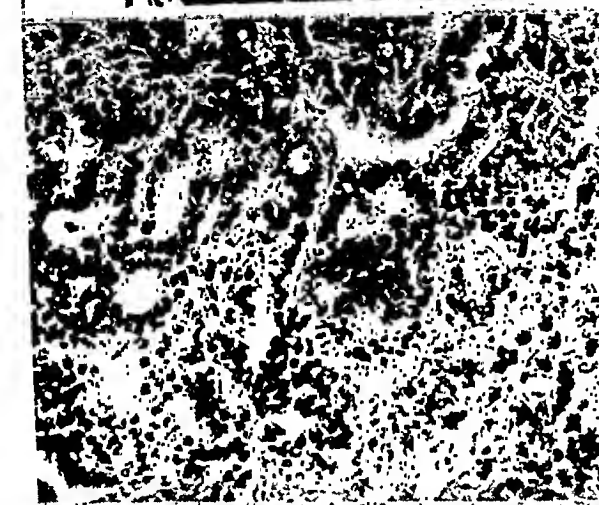


FIG. 16

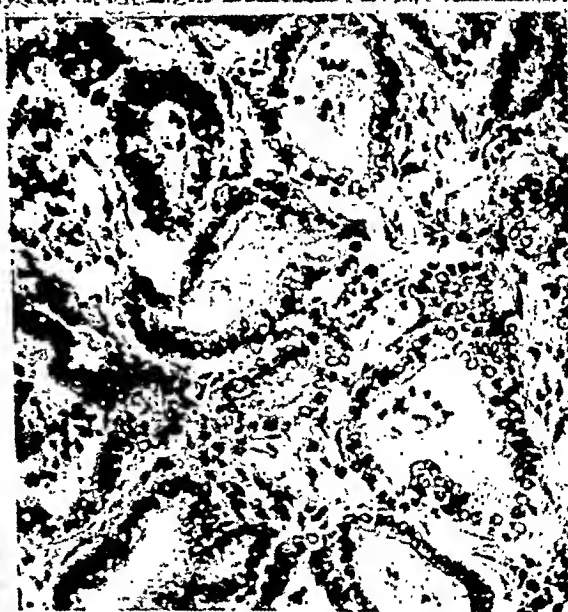
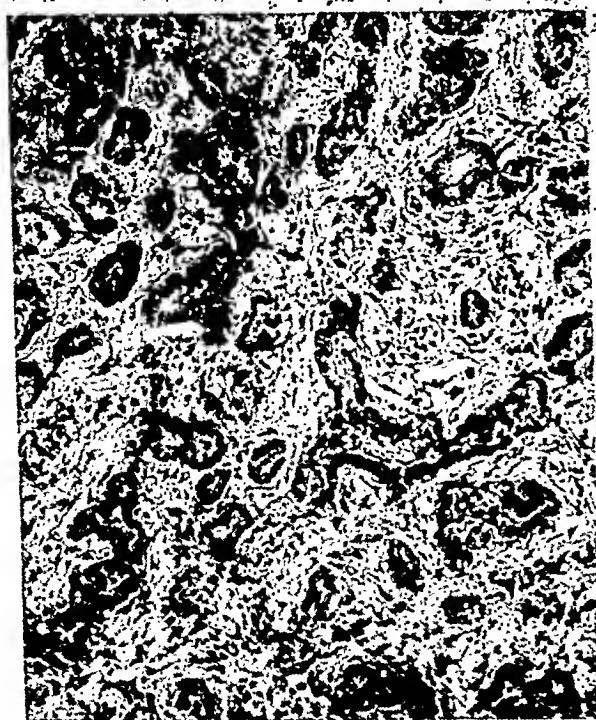


FIG. 17

FIG. 18

FIG. 13.—No. 294: Gross appearance of animal at autopsy.

FIG. 14.—No. 294: Growth of tumor in the liver.

FIG. 15.—No. 294: Metastasis in the lung.

FIG. 16.—No. 678: Growth of tumor in the gallbladder wall.

FIGS. 17-18.—No. 678: Metastatic growth in the mediastinum.

No. 678.—*Experiment 5:* Sterile glass tube. Tumor found 14 months after experimental procedure. Hypertrophy of gallbladder wall, with atypical epithelial proliferations into muscle. Metastases to mediastinum. *Histologic Diagnosis:* Adenocarcinoma (Figs. 16-18).

The incidence of 10 per cent, if it is allowable to derive percentages from such small numbers, is higher than that noted in most statistics on the incidence of cancer of the gallbladder in human beings suffering from gallstones. Among 378 cases of cholelithiasis at the Obukhov hospital, in Leningrad, cancer of the gallbladder occurred in 15, or approximately 4 per cent. According to Lentze,⁸ among 557 cases of cholelithiasis in women over 40 years of age, 5 per cent had cancer. Luelsdorf,⁹ at necropsy, found cancer of the gallbladder in 56 of 892 cases of cholelithiasis, or 6.2 per cent. Graham¹⁰ gave 8.2 per cent for the material at the Barnes hospital, and 10 per cent for the cases of Mayo-Robson.

TABLE I
INTRODUCTION OF FOREIGN BODIES INTO GALLBLADDERS OF GUINEA-PIGS

Exper. No.	Foreign Body	Number Operated Animals	Number Animals Surviving Over 14 Months	Number Animals With Epithelial Hyperplasia of Gallbladder	Number Animals With Malignant Tumors	Number Animals With Metastases
1	Gallstones.	17	4	12		
	Crude paraffin.	5		2		
	Saprol	4		3		
	Shale	2		2		
2	Glass tubes containing 1γ radium	12	8	9	2	1
3	Glass tubes, sterile, 10-16x2 mm.	7	6	6	2	2
4	Glass tubes, sterile, 10-16x2 mm.	17	9	1*		
5	Glass tubes, sterile, 10-16x2 mm.	22	11	7	1	1
6	Glass tubes, sterile, 10-16x2 mm.	8†	7	4		
7	Glass tubes, paraffined, and powdered with infusorial earth.	6‡	6	6		
Total.		100	51	52‡	5	4

* Histologic examination lacking in many cases.

† Animals of Experiment 6, and 2 animals of Experiment 7 received subcutaneously 400 mg. of o-aminotoluene during 3.5 months.

‡ Beginning at 2 months.

In statistics from various sources gathered by us in 1928, the occurrence of gallstones in primary cancer of the gallbladder in man is a general rule. Stones were found in 70 to 100 per cent of the total of 785 cases. On the other hand, Graham¹⁰ found only three cases of cholelithiasis in 38 cases of secondary, or metastatic, carcinoma of the gallbladder.

It is concluded from these data that in the association of gallstones and cancer of the gallbladder, the rôle of the stones is primary. This furnishes special interest to the experimental attempts to produce cancer of the gallbladder following the introduction of hard foreign bodies into the viscus.

In regard to the experimental animals, it appears that the strictest requirements are met by guinea-pigs. According to Warren and Gates,¹¹ spontaneous cancer of the gallbladder has not been described in guinea-pigs.

Table I and the photomicrographs show that our results substantiate the possibility that sterile hard foreign bodies introduced into the gallbladder produce an hyperplastic growth of the epithelium in a large percentage of cases, and malignant epithelial proliferation, with local invasion and metastases, in a considerably smaller percentage.

The mechanism of this process is not evident. Most probably, the essential reaction consists of secondary degeneration and regeneration of the epithelium, caused by the foreign bodies. It is also possible to postulate a chemical carcinogenic effect in the stagnant bile and its products of decomposition. Factors of hereditary predisposition to cancerous growth also must play a rôle.

Another comment should be made, on the practically incurable nature of cancer of the gallbladder in man. Surgical removal is possible only in rare cases.¹² Radiation therapy is apparently entirely unsuccessful. Therefore, the only available method against this condition is prophylactic cholecystectomy in cholelithiasis, especially in women over 40 years of age. This conclusion was reached by Graham long ago, and he rightly stated that the danger of cancer of the gallbladder in such cases is greater than the operative risk in cholecystectomy when it is not complicated by jaundice.

SUMMARY AND CONCLUSIONS

Table I presents data on the introduction of sterile, hard, foreign bodies into the gallbladders of 100 guinea-pigs, of which 51 animals survived 14 months or longer. In five animals, after 14 to 39 months, there was found an epithelial proliferation of the gallbladder wall, with characteristics of malignant growth; local invasion in five, metastases to distant organs in four, and complete destruction of the gallbladder, with hemorrhage in serous cavities, in two. Photomicrographs of these observations are shown.

The development of malignant growth following the introduction of hard foreign bodies into the gallbladder is established. In guinea-pigs, the process requires over one and sometimes over two years.

The desirability of prophylactic cholecystectomy for gallstones in elderly women, as advocated by Graham, receives experimental support. The highly malignant course of cancer of the gallbladder, established by observations on man, is also confirmed by our experiments on guinea-pigs.

REFERENCES

- ¹ Petrov, N. N., and Krotkina, N. A.: Experimentelles Gallenblasen und Leberkarzinom. *Ztschr. f. Krebsforsch.*, 38, 249-263, 1933.
- ² Lam, C. R.: The Present Status of Carcinoma of the Gallbladder. *ANNALS OF SURGERY*, 111, 403-410, 1940.
- ³ Lazarus-Barlow, W. S.: An Attempt at the Experimental Production of Carcinoma by Radium. *Proc. Roy. Soc., London, ser. Path.*, 11, 1-17, 1918.
- ⁴ Kazama, Y.: Studies on Artificial Production of Tumors in Viscera. *Japan M. World*, 2, 309-312, 1922.
- ⁵ Leitch, A.: Gallstones and Cancer of the Gallbladder: An Experimental Study. *Brit. M. J.*, 2, 451-454, 1924.

- ⁶ Creighton, C.: Correspondence regarding Leitch's article. *Brit. M. J.*, **2**, 1079, 1924.
- ⁷ Rouillard, J.: Experimental Cancer of Gallbladder. *Presse med.*, **33**, 1014-1015, 1925.
- ⁸ Lentze, F. A.: Gallstones and Carcinoma of Gallbladder. *Beitr. z. klin. Chir.*, **137**, 38-62, 1926.
- ⁹ Luelsdorf, F.: Beziehungen zwischen Steinkrankheit und Krebs der Gallenblase. *Ztschr. f. Krebsforsch.*, **24**, 395-405, 1927.
- ¹⁰ Graham, E. A.: Prevention of Carcinoma of Gallbladder. *ANNALS OF SURGERY*, **93**, 317-322, 1931.
- ¹¹ Warren, S., and Gates, O.: Spontaneous and Induced Tumors of the Guinea-pig. *Cancer Research*, **1**, 65-68, 1941.
- ¹² Aiga, Y.: Über einen selten Fall von operativ dauernd geheilten Gallenblasenkarzinom. *Zentralbl. f. Chir.*, **62**, 212-215, 1935.

ANNOUNCEMENT

UROLOGY AWARD

The American Urological Association offers an annual award "not to exceed \$500" for an essay (or essays) on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

For full particulars write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee. Essays must be in his hands before May 1, 1947.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Buffalo, New York, June 30-July 3, 1947.

Committee on Scientific Research,

MILEY B. WESSON, *Chairman*,
JUDSON B. GILBERT
ANSON L. CLARK

BRIEF COMMUNICATIONS

LARGE MELENA CAUSED BY SPONGE ULCERATING INTO LUMEN OF ILEUM MORE THAN TWENTY YEARS AFTER CELIOTOMY

HARRY C. SALTZSTEIN, M.D.

AND

JOHN O. RAO, M.D.

DETROIT, MICHIGAN

Case Report.—Catherine G., age 56, was admitted to the hospital in August, 1945, with a diagnosis of abdominal carcinoma. She had had a celiotomy for a pelvic complaint 25 years before, and an emergency celiotomy for bowel obstruction two and one-half years later. She had then been apparently well until 1939. In 1940, a diagnosis of duodenal ulcer was made and she was put on a diet. Occasional epigastric pain and eructations, with flatulence, experienced since that time, always responded to an ulcer regimen of diet, alkalies, *etc.*

On May 21, 1945, the patient was seized with a sudden attack of fainting, and passed a large amount of dark blood per rectum. She felt nauseated, seemed to taste blood, but never vomited. Frequent tarry stools occurred almost daily. Following four or five weeks of this, she was hospitalized at another institution. Their findings showed low blood pressure (95/60), some shock (which was remedied with blood transfusions), and a palpable movable mass, 3 x 4 inches in diameter, low and slightly to the left of the umbilicus. Roentgenograms of the stomach revealed no evidence of pathology. A barium enema filled the entire colon. The possibility of an extracolonic mass in the lower left abdomen was considered, although the small bowel was not roentgenographed. Discharged after a few days, she had another severe hemorrhage from the rectum within a week and was readmitted to the same hospital July 16, 1945. The stomach and duodenum were again roentgenographed, with negative findings. No source of bleeding was found. Chest roentgenographs and gastric analysis were suggested, and one consultant suggested celiotomy for suspected carcinoma, though this was not done.

The patient was transferred August 9, 1945, with the following diagnosis on the transfer chart: "Pelvic tumor with fixation to the bowel which causes the hemorrhage. May have to resect bowel."

When admitted, the patient was a very pale and bled-out woman, otherwise alert and active. Hemoglobin 3.5 Gm., or 21 per cent; R. B. C. 1,430,000. After repeated transfusions the hemoglobin finally went to 41 per cent (7.3 Gm.); R. B. C. 2,280,000. At times a mass could be felt in the left lower or midabdomen, but at other times it was absent. A barium enema stopped in the lower sigmoid. It was decided to explore the abdomen. *Clinical Diagnosis:* Far-advanced carcinoma of the sigmoid.

Exploration revealed a normal thin sigmoid colon, free and clear throughout. In the lower reaches of the ileum, there was a mass the size of a small orange which consisted of three matted loops of small bowel, plastered against a cyst-like, cheesy, inspissated mass. One loop of small bowel was easily detached, the second was so involved that the serosa along one side had been destroyed, and the third was intimately attached. There was an ulceration 1 cm. in diameter connecting the lumen of this loop of small bowel with the mass.

Upon further dissection, the mass was peeled away from the mesentery with a pseudocyst wall. It was not a dermoid, but, in the center was an old celiotomy sponge, still recognizable as such, in spite of an advanced stage of disintegration. Bleeding had been caused by the ulceration into the small bowel.

The ulcer was trimmed and closed, and the second loop, where the serosa was destroyed, was excised and reanastomosed. The patient made an uneventful recovery. Examination, January 12, 1946, disclosed her condition to be excellent, with no complaints, and bowel movements normal.

COMMENT.—Some 250 cases where a sponge had been left in the abdomen following a celiotomy were analyzed in 1940 by Crossen and Crossen. The clinical symptomology, as developed by them from this material, is briefly as follows: During the first month, the sponge is incidental to the inflammation and may suppurate and discharge through the incision or gravitate into the pelvis and rupture into the rectum with the abscess. After two or three months the acute inflammation subsides and the sponge, now a foreign body, may extrude, as such, through a sinus opening either externally or into the bowel, bladder or vagina.

When two or three years have passed, the sponge is well-encapsulated, and often exists harmlessly in the peritoneal cavity. After five years, the capsule becomes thin, and the mass seems like a dermoid or caseated node. Though it does not calcify, the sponge fibers resist disintegration and, even in very late stages, the sponge can be recognized as such.

Only 14 of these 250 cases were found five years or more, after the original operation. Four were found after 15 years.

Extrusion into the bowel lumen occurred in 28 per cent of the total cases, usually within the first ten months. The sponge was found entirely within the small bowel in about one-third of these. Symptoms of extrusion of the sponge into the bowel lumen were indigestion and obstruction; *i.e.*, mild pains at irregular intervals grading into violent colics, with vomiting. Emergency operations for intestinal obstruction had had to be performed. None of the case reports they reviewed showed gross blood or serious bleeding into the bowel lumen.

Harvey Stone reported 71 cases where many different sorts of intestinal lesions produced large melena of obscure origin, though in no instance was ulceration of an old celiotomy sponge into the intestinal canal listed as having caused severe gastro-intestinal hemorrhage.

However, very small lesions in the jejunum or ileum may cause severe intestinal bleeding. Segal and Merle Scott have recently called attention to this, and stress the fact that these cases mimic bleeding ulcer.

SUMMARY

A case is reported in which a sponge ulcerating into the ileum 25 years after celiotomy caused severe gastro-intestinal hemorrhage.

REFERENCES

- 1 Crossen, H. H., and Crossen, D. F.: Foreign Bodies Left in Abdomen. Mosby, 1940, St. Louis.
- 2 Segal, H. L., and Scott, W. J. Merle: Massive Hemorrhage from Small Intestine. J. A. M. A., 129, 116, September 8, 1945.
- 3 Stone, Harvey B.: Large Melena of Obscure Origin. ANNALS OF SURGERY, 120, 582, October, 1944.

PERFORATED CARCINOMA OF THE LARGE INTESTINE COMPLICATING PREGNANCY*

SUCCESSFUL OPERATIVE MANAGEMENT

W. B. SWARTLEY, M.D., Z. B. NEWTON, M.D., J. C. HARTMAN, M.D.

AND

J. W. STAYMAN, JR., M.D.

PHILADELPHIA, PA.

CARCINOMA of the large intestine during pregnancy requires the most careful surgical judgment in its management. The condition is a rare one, and each case demands especial evaluation because of the variable factors involved. However, in dealing with these cases certain underlying principles are to be kept in mind.

First, as Banner, *et al.*, stated in 1945, the question as to the best management for saving both mother and child must be answered. And if one of the pair has little, if any, chance of survival, how can the life of the other best be protected?

Second, the fact that pregnant women tolerate major surgical procedures as well as the nonpregnant has been brought out by Child and Douglas, in 1944, and reëmphasized by Finn and Lord, in 1945.

Third, the increased danger of peritonitis during pregnancy has long been known. In the series of Child and Douglas the maternal mortality rate was 66 per cent. The infant mortality is also increased, and labor is likely to be precipitated.

With these principles in mind, the approach to a given case of carcinoma of the large intestine during pregnancy is made less difficult. There is nearly unanimous agreement that in the early months of pregnancy the management of the malignancy should be the same as if the patient were not pregnant. Immediate termination of the pregnancy has been recommended by Adair, in 1940, on the basis that pregnancy increases the rate of growth of malignancy. However, there is not enough evidence to support the idea that pregnancy effects an extragenital malignancy to such an extent that it warrants termination.

In the latter months of pregnancy, with a viable fetus, the management is somewhat more difficult. Banner, *et al.*, seem to have the most logical approach to this problem. They recommend exploratory celiotomy to determine the operability of the lesion as soon as possible. If the lesion is inoperable and does not obstruct the birth canal, simple colostomy is done to permit normal delivery. If the lesion is operable, cesarean section, hysterectomy, followed by resection of the lesion is indicated. When the lesion is in the transverse colon and can be exteriorized, it may be possible to perform a stage-resection without entering the pelvis, thereby, permitting a normal delivery.

* Presented before the Philadelphia Academy of Surgery, May 6, 1946.

Unfortunately, pregnancy may mask the symptoms of carcinoma of the large intestine and the lesion may progress to obstruction or perforation before it is recognized. In these cases the management is most difficult. Berkeley, Bonney, and MacLeod, in 1938, outlined the management for cases with obstruction. They recommend hysterotomy, colostomy, and later resection, regardless of the stage of pregnancy. DerBrucke, in 1940, reported two cases of obstruction from carcinoma of the colon in pregnancy. He states that at that time a total of seven cases of obstruction of the colon from carcinoma were on record, and that only three of these cases were due to carcinoma of the colon:

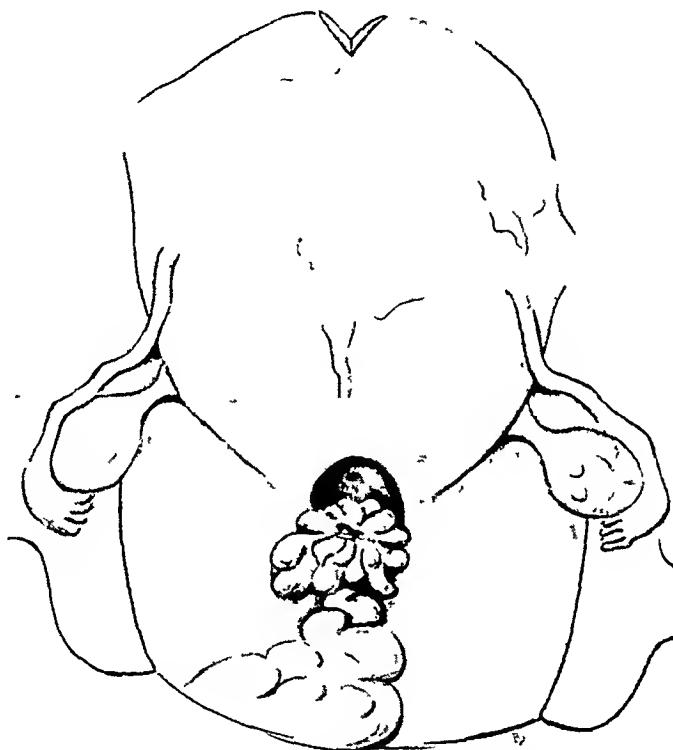


FIG. 1.—Diagram of pelvis at operation showing previously opened uterus containing fibroids, and carcinoma with perforation.

three were carcinoma of the ovary and one was carcinoma of the ileum. He recommends induction, with delivery from below, followed by celiotomy. Of the seven cases he reported the maternal mortality was 66 per cent and the infant mortality was 28 per cent. Finn and Lord, in 1945, reported the successful operative management of an obstructive carcinoma of the sigmoid colon in a six-month-pregnant woman. The tumor was removed by a three-stage procedure, and the patient subsequently had a normal delivery. They state that the pregnant uterus did not interfere significantly with the technical performance of the operation, and they support the statement of Child and Douglas: "Pregnant women tolerate even major surgical procedures quite as well as the nonpregnant."

three were carcinoma of the ovary and one was carcinoma of the ileum. He recommends induction, with delivery from below, followed by celiotomy. Of the seven cases he reported the maternal mortality was 66 per cent and the infant mortality was 28 per cent. Finn and Lord, in 1945, reported the successful operative management of an obstructive carcinoma of the sigmoid colon in a six-month-pregnant woman. The tumor was removed by a three-stage procedure, and the patient subsequently had a normal delivery. They state that the pregnant uterus did not interfere significantly with the technical performance of the operation, and they support the statement of Child and Douglas: "Pregnant women tolerate even major surgical procedures quite as well as the nonpregnant."

Fig. 1.—Diagram of pelvis at operation showing previously opened uterus containing fibroids, and carcinoma with perforation.



Unfortunately, pregnancy may mask the symptoms of carcinoma of the large intestine and the lesion may progress to obstruction or perforation before it is recognized. In these cases the management is most difficult. Berkeley, Bonney, and MacLeod, in 1938, outlined the management for cases with obstruction. They recommend hysterectomy, colostomy, and later resection, regardless of the stage of pregnancy. DerBrucke, in 1940, reported two cases of obstruction from carcinoma of the colon in pregnancy. He states that at that time a total of seven cases of obstruction of the colon from carcinoma were on record, and that only three of these cases were due to carcinoma of the colon:

found. A cecostomy was performed and the abdomen was drained. The patient died 12 hours later. Autopsy revealed a perforated carcinoma of the rectum.

According to Banner, *et al.*, there were 62 reported cases of carcinoma of the intestine complicating pregnancy up until 1943. They have added seven cases in 1945, Finn and Lord have reported one case, in 1945, and with the addition of this case the total number of reported cases is 71.

Case Report.—Mrs. C. T., a 39-year-old, white, primipara, was admitted to the Germantown Hospital Obstetrical Service, September 29, 1945, with the chief complaint of pregnancy, approximately seven and one-half months, associated with the sudden onset of lower abdominal, colicky pain, nausea and fever.

Her history dates back approximately two years, at which time she noticed increasing diarrhea and tenesmus. This condition progressed for one year, when she consulted a physician because of the appearance of blood and mucus in the stools and a weight loss from 128 to 113 pounds. She was told that she had "colitis" and was given medication. She was married shortly thereafter, and soon became pregnant. Following pregnancy the symptoms of "colitis" became more pronounced and she again consulted a physician in April of 1945. At this time the following studies were made: gastric analysis, stool examination, and barium enema. She states that she was given a sulfa drug and a nonresidue diet; and that she had no more progression of symptoms until the time of her admission. Her weight gain with pregnancy was 113 to 130 pounds; and her expectant date of delivery was November 10, 1945. There were no other significant facts in her history.

Physical examination was essentially negative except for the abdomen which revealed a nodular, pregnant uterus, seven to eight months, and bilateral lower abdominal tenderness. On rectal examination, a hard tumor mass could be palpated with the tip of the examining finger and there was considerable tenderness in the cul-de-sac. On admission, the temperature was 100° F; pulse 96; and respirations 20. Blood count: Hb. 85 per cent, R. B. C. 4,300,000; W. B. C. 23,400.

A surgical consultation was ordered, October 1, 1945, and the patient was proctoscoped. At the 10-cm. level a crater-like tumor was visualized which grossly appeared malignant. In view of the patient's acute symptoms and the proctoscopic findings, celiotomy was immediately decided upon.

Operation.—October 1, 1945: Under continuous spinal anesthesia, the abdomen was opened through a low midline incision, and a pregnant uterus containing several fibroids was encountered. A classical cesarean section was performed and a five and one-half-pound, living, male child was delivered. The liver was palpated and there was no evidence of metastatic growth. In the pelvis there was free pus, with marked inflammation and induration of the pelvic tissues (Fig. 1). There was a palpable tumor in the region of the rectosigmoid which was adherent to the surrounding tissues and contained a perforation. A subtotal hysterectomy, left salpingoophorectomy, and first-stage Lahey bowel resection were performed (Fig. 2). The abdomen was closed, with drainage in the pelvis. Operating time: one hour.

The patient withstood the operation well, and ran a normal postoperative course. She was given blood, fluids, sulfadiazine, and all necessary supportive therapy. She was discharged in good condition on the 32nd day. At home the patient improved. She gained weight and strength and her wounds healed satisfactorily.

She was readmitted one month later, December 3, 1945, and was immediately prepared for operation with blood transfusions and sulfathaladine. She was operated upon on December 5, 1945, under continuous spinal anesthesia. Exploration of the upper abdomen and liver again revealed no evidence of metastasis. In the pelvis the inflammatory reaction

had subsided considerably. The tumor in the rectosigmoid was present and was adherent to the surrounding tissues. An abdominoperineal resection was performed with considerable difficulty because of the adherent tumor. The patient withstood the operative procedure well.

The specimen consisted of sigmoid, rectum, and anus, with adjacent fat and enlarged lymph nodes. There was an annular carcinoma, with perforation in the region of the rectosigmoid junction. Microscopic examination of the specimen revealed adenocarcinoma (Fig. 3). There was no microscopic evidence of lymph node involvement in the mesentery.



FIG. 3.—Photomicrograph of adenocarcinoma removed at operation.

The patient's postoperative course was favorable, and she was discharged on the 35th day. Since discharge the patient has gained weight and strength. Her wounds have healed well and her colostomy functions satisfactorily. Her weight on discharge was 88 pounds and is now 123. The child is likewise in good condition, weighing 20 pounds.

DISCUSSION.—We attribute the success in this case to the recognition of the principles mentioned earlier in this paper, modern pre- and postoperative care, chemotherapy, and the excellent coöperation between the Surgical and Obstetrical Departments.

This patient was in acute distress, and celiotomy was unquestionably indicated. With a viable fetus, cesarean section appeared to be the first logical

move. Had not cesarean section been performed we believe that this patient would have gone into labor as a result of peritonitis, and that both mother and child would have been subjected to a greater risk. Hysterectomy was carried out for the following reasons: to prevent infection of the open uterine sinuses in the presence of an already infected pelvis, to facilitate drainage of the pelvis, to allow greater exposure for the subsequent bowel resection, and to remove a uterus diseased with fibroids. The carcinoma was attacked in two stages because we feel that it would have been considerable added risk, and technically more difficult, to perform an abdominoperineal resection at the first operation. The prognosis in this case is to be guarded, as is the prognosis in all cases of perforated carcinoma of the large intestine. From a review of the literature, we find this to be the third case of perforated carcinoma of the large intestine complicating pregnancy, and the first case in which both mother and child have survived.

SUMMARY

1. The literature has been reviewed with respect to carcinoma of the large intestine complicating pregnancy.
2. A case of perforated carcinoma of the rectum complicating pregnancy is reported.
3. The principles of the management of such a case are outlined.

REFERENCES

- ¹ Adair, F. L.: *Obstetrics and Gynecology*. Vol. 2, P. 623, Philadelphia: Lea and Febiger, 1940.
- ² Banner, E. A., Hunt, A. B., and Dixon, C. F.: *Surg. Gynec. Obst.*, 80, 211, 1945.
- ³ Berkeley, C., Bonney, V., and MacLeod, D.: *The Abnormal in Obstetrics*. P. 120, London. Edward Arnold and Co., 1938.
- ⁴ Child, C., and Douglas, R. G.: *Am. J. Obst.*, 47, 213, 1944.
- ⁵ DerBrucke, M.: *Am. J. Obst.*, 40, 307, 1940.
- ⁶ Finn, W. F., and Lord, J. W.: *Surg. Gynec. Obst.*, 80, 545, 1945.
- ⁷ Fournier, R.: *Bull. Soc. Obst. Gynec.*, Paris, 26, 241, 1937.
- ⁸ Mengert, W. F.: *Am. J. Obst.*, 26, 451, 1933.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.



THE SURGICAL THERAPEUTIC SIGNIFICANCE OF THE FUNCTIONAL BEHAVIOR OF THYROID NODULES*

I. DARIN PUPPEL, M.D., CHARLES P. LEBLOND, M.D., AND
GEORGE M. CURTIS, M.D.

COLUMBUS, OHIO

FROM THE DEPARTMENT OF RESEARCH SURGERY OF THE OHIO STATE UNIVERSITY, COLUMBUS, OHIO

THE EXACT FUNCTION of thyroid nodules or adenomas has not been completely established in spite of much work which has been done in an attempt to elucidate the problem. Most of the nodules are believed to originate from an abnormal hyperplasia-involution cycle.^{1, 2} However, there are two schools of thought regarding the origin of the so-called fetal adenoma. One group, including Beck,³ Wölfler,⁴ Ribbert,⁵ and others, contends that fetal adenoma arises from multiple embryonal cell nests scattered through the thyroid tissue. On the other hand, according to the hypothesis of Virchow,⁶ Hitzig,⁷ Michaud,⁸ and others, which has been preferred by many modern workers, the fetal adenoma develops from the normal adult thyroid epithelium. Some even have postulated that the fetal adenoma is a growth of small acini into preëxisting colloid of a follicle.⁹ At times it is difficult to differentiate between the usual nodule and a fetal adenoma so that investigators have called all these tissues either nodules, adenomatous nodules or adenomas of the thyroid gland. As a matter of fact, Boyd¹⁰ stated that many of the nodules which have been regarded as fetal in type are essentially only varieties of the colloid adenoma, since both may be seen shading into the other in a single section.

When an adenoma of endocrine gland tissue occurs, the tumor in certain instances is known actually to function as secretory tissue, as is noted in the hypoglycemia produced by an adenoma of the islets of Langerhans of the pancreas and the hypercalcemia due to an adenoma of the parathyroid gland. In other endocrine glands, such as the thyroid, it has been questioned as to whether adenomas may also cause symptoms, or whether they exist without producing any manifestations of functional activity. Much thought has also been given to such questions as to whether the nodular or the paranodular goitrous tissue is responsible for the hyperthyroidism in the patient with toxic nodular goiter, as to whether the nodules of nodular goiter are even capable of functioning, and as to why large amounts of adenomatous tissue may often be removed from the patient with nontoxic nodular goiter without producing

* Aided by a grant from the Comly Fund for Research of the Ohio State University, Columbus, Ohio.

appreciable change in the clinical thyroid function or in the basal rate of metabolism, and from the patient with toxic nodular goiter without producing postoperative hypothyroidism.

A number of pathologists and investigators confusing the parenchymatous appearance of some nodules or of some paranodular tissue with that of hyperactive thyroid tissue in which there is also a predominance of epithelial over colloid material, were led to believe that these nodules were also made of hyperactive thyroid tissue. However, further investigation revealed that the nodules, paranodular tissue, or both may show evidences of hyperplasia in a certain number of cases of nontoxic nodular goiter. We now know that the presence of hyperplasia or hypertrophy cannot be considered a definite criterion of the presence of clinical hyperthyroidism. Johnson,¹¹ in 1939, reported that 19 per cent of all nodules of nontoxic nodular goiter show hypertrophy and only 37.4 per cent of the nodules of toxic nodular goiter show similar hypertrophy.

The surgeons have also tried to solve this problem by simple enucleation of a so-called hyperfunctioning adenoma. Parsons,¹² of Columbia University, in 1927, and others, have reported amelioration of toxic symptoms after such surgery. At first thought this would indicate that the adenomatous tissue, *per se*, had been the cause of the hyperfunction. On the other hand, Holst,¹³ and others, have reported similar dramatic amelioration of the hypothyroid state after enucleation of a single adenoma. Why such patients with hyperthyroidism or hypothyroidism return to a euthyroid state after thyroid surgery still remains unknown. May it be that the adenomatous tissue stimulates the surrounding tissue to hyperfunction in one instance and inhibits it to hypofunction in another instance and with removal of the adenomatous tissue there is amelioration of symptoms? These surgical end-results may also be related to other factors than the surgery, *per se*, perhaps to factors in the preoperative or postoperative care. Furthermore, it should be emphasized that after such simple enucleation the chances for recurrence of the symptoms are greater, as was pointed out years ago by Parsons,¹² so that bilateral subtotal thyroidectomy is now considered the operation of choice by many for at least the usual case of toxic nodular goiter.

Marine¹⁴ reported, in 1912, that fetal, intermediate and simple adenomas contained almost invariably smaller amounts of iodine than the surrounding nontumor thyroid. He did not differentiate toxic from nontoxic goiter. Wegelin¹⁵ later found that adenomatous tissue fed to tadpoles exerted less effect on growth than the surrounding thyroid tissue. Branovacky,¹⁶ also using Gudernatch's tadpole test, found that the tissue from the nodular element in secondary toxic goiter was rather more active than the internodular tissue.

Because methods of determining the functional behavior of various parts of a nodular goiter, heretofore, have been so equivocal and inadequate, we have felt that radioiodine may be of help in solving this problem. Recently, a group of us, Dr. George M. Curtis, Dr. Charles P. Leblond, Miss Elsie Riley, Mrs. Martha Radike, and I, made radioiodine and ordinary iodine fractionation studies¹⁷ of many forms of pathologic thyroid tissue removed from seven patients with various clinical types of goiter and varying degrees of toxicity.

These data indicate that the cells of all types of nodular or adenomatous thyroid tissue thus far studied are functionally autonomous and consistently produce less thyroxine and diiodotyrosine, and show less avidity for iodine than the groups of thyroid cells in the surrounding tissue. The biochemical aspects of the problem have already been set forth.¹⁷ We now wish to present the clinical and surgicopathologic background together with a detailed correlation between the various phases of the work as well as the probable surgical significance of the findings.

EXPERIMENTAL METHODS

During the preoperative period several determinations of the basal metabolic rate were made. Repeated determinations of the acetone-soluble and insoluble iodine fractions of the blood were also carried out. None of these patients received iodine in the immediate preoperative period other than a minimal (two micrograms) given just before operation with the radioiodine solution. Actual preparation of the hyperthyroid patients for thyroidectomy included general measures, such as adequate mental and physical rest, adequate sedation, a well-balanced diet of high carbohydrate, high protein, high vitamin and high caloric content, as well as calcium, phosphorus and vitamin D in sufficient doses and treatment of existing complications.¹⁸ None had received thiouracil. One (L. D.), was known to have received iodine at home up to five weeks prior to operation.

A solution of radioiodine containing 25 to 1,000 microcuries of the radioactive element I^{131} and about 2 micrograms of ordinary iodine I^{127} was administered 15 to 23 hours before thyroidectomy, with the exception of R. G., when 40 hours intervened between the administration and operation. The small iodine content of the solution of radioactive iodine insured that a true picture of the physiologic behavior of iodine would be given by studies with radioiodine.

Blood was drawn during operation (15 to 20 hours after ingestion of radioiodine) from one patient with nontoxic and from one with toxic goiter. This showed no detectable radioiodine in organic combination. We have, therefore, assumed that the radioiodine present in organic combination in each thyroid gland represents a nearly true picture of the ability of that gland to produce physiologically active organic iodine compounds. However, these data are too few and further investigation of this phase of the methods used is necessary.

An idea of the total thyroid weight was gained by recording the weight of the goitrous tissue removed and estimating the amount of thyroid tissue left behind. For study of the nodular goiters we chose large and representative sections of as well-circumscribed nodules as possible which were in appearance quite similar to the other nodules present. A representative portion of the surrounding or paranodular thyroid tissue was also carefully selected for study. A portion of each selected tissue was given to the biochemist for determination of radioactivity and of ordinary iodine. The other portion was serially sectioned for microscopic study.

Determinations of ordinary iodine I^{127} and radioiodine I^{131} were performed in the various iodine fractions of both the nodules and the surrounding thyroid tissue. The inorganic iodine, the diiodotyrosine iodine, and the thyroxine iodine were separated after a method used by Mann, Leblond and Warren.¹⁹ A portion of the solution of each fraction was used to determine iodine I^{127} by a wet ash method,²⁰ with slight modification. Another portion of the solution was used for measurement of the radioactivity by the Geiger counter. Details of biochemical methods used have already been presented.¹⁷

The microscopic sections shown are quantitatively the most representative of the serial sections studied.

RADIOACTIVE IODINE INGESTION

Seven patients with various diseases of the thyroid gland were given radioactive iodine by mouth, thyroidectomized, and the removed goiters were investigated grossly, microscopically and biochemically. The protocols may be reviewed briefly as follows:

REVIEWS OF PROTOCOLS

Protocol of M. H.—No. 445260, with Nontoxic Diffuse Colloid Goiter and a Fetal Adenoma: M. H., a colored schoolgirl, age 15, entered University Hospital, June 19, 1944, for surgical treatment of a nodular goiter.

She had enjoyed entirely good health up to about six months ago when she first became aware of a lump in the right neck anteriorly. This gradually grew outward, producing a tumor so unsightly as to lead the patient and her family to request its removal for cosmetic reasons. There were no pressure symptoms related to breathing or swallowing. No toxic symptoms occurred, such as tachycardia, tremor of the fingers or exophthalmos. No known iodine treatment had been given. Measles and mumps occurred in childhood. She had no other illnesses except for frequent sore throat. Past history and inventory by systems were otherwise negative. One sister had goiter.

Physical examination disclosed a well-developed and well-nourished colored girl, age 15, lying quietly in bed in no acute distress. Skin was of normal warmth and moisture. Eyes protruded normally, the exophthalmometric reading being 14 mm. for each eye, which is normal. Few carious teeth were present. The tongue presented no tremor. The oropharynx was clear. The tonsils were slightly enlarged and a few infected follicles were present. Examination of the neck revealed a bilateral, diffuse soft enlargement of the thyroid which was not very marked. However, in the midportion of the right lobe there was also a large hard nodule which felt smooth. It protruded for about two inches, thus constituting a cosmetic blemish. This moved with deglutition. The trachea was in the midline. The extended and abducted fingers showed no tremor.

Admission red blood count was 4,300,000, with the hemoglobin 13.6 Gm. per cent. The white blood cell count was 8,400, with neutrophils 60 per cent, lymphocytes 37 per cent, monocytes 1 per cent, and eosinophils 2 per cent. Urinalysis was negative. Blood Mazzini and Kahn reactions were negative. The basal metabolic rate on June 20 was plus 7 per cent, with the temperature 98.4°F., pulse 72, and respirations 12. A basal metabolic rate determination on June 22 was minus 2 per cent, with the temperature 98.2°F., pulse 72, and respirations 19. The total blood iodine averaged 4.88 and the acetone insoluble fraction 1.30 micrograms per cent, which are normal. Fluoroscopy of the chest and neck revealed the trachea in the midline, and no retrotracheal extension of the goiter. No intrathoracic extension was noted. Otherwise, fluoroscopy was negative. Indirect laryngoscopy showed both vocal cords normal in appearance and function.

Radioactive iodine was given in grape juice at 1:00 P.M. on June 22, 1944. Morphine,

BEHAVIOR OF THYROID NODULES

gr. $\frac{1}{8}$, and scopolamine, gr. $\frac{1}{300}$ were given pre-anesthetically. Usual skin preparation was made with tincture of quaternin. Usual draping was carried out.

Under avertin, 80 mg. per kilo per rectum, as well as cyclopropane, oxygen and helium anesthesia, a right partial thyroidectomy was done by one of us (I. D. P.) at 9:00 A.M. on June 23, 1944. The large nodule of the right lobe was removed together with a minimal amount of diffuse tissue. The remaining portions of the thyroid gland were left alone because we felt that this was a manifestation of diffuse goiter occurring in an endemic area during adolescence and that it could be treated adequately by administration of iodine.

The right thyroid lobe as removed measured $4.5 \times 3.5 \times 3.5$ cm., and weighed 18 Gm. It contained one large nodule. On cross-section, the nodule measured 3 cm. in diameter. It was sharply circumscribed and encapsulated by a thin wall of fibrous tissue. It consisted of a fairly solid, light tan material of uniform appearance which contained very little colloid. The extranodular tissue was diffuse in character and on cross-section presented a uniform appearance associated with the presence of an excess amount of colloid. Microscopically (Fig. 1A), the nodule showed a typical fetal adenoma with the acini very

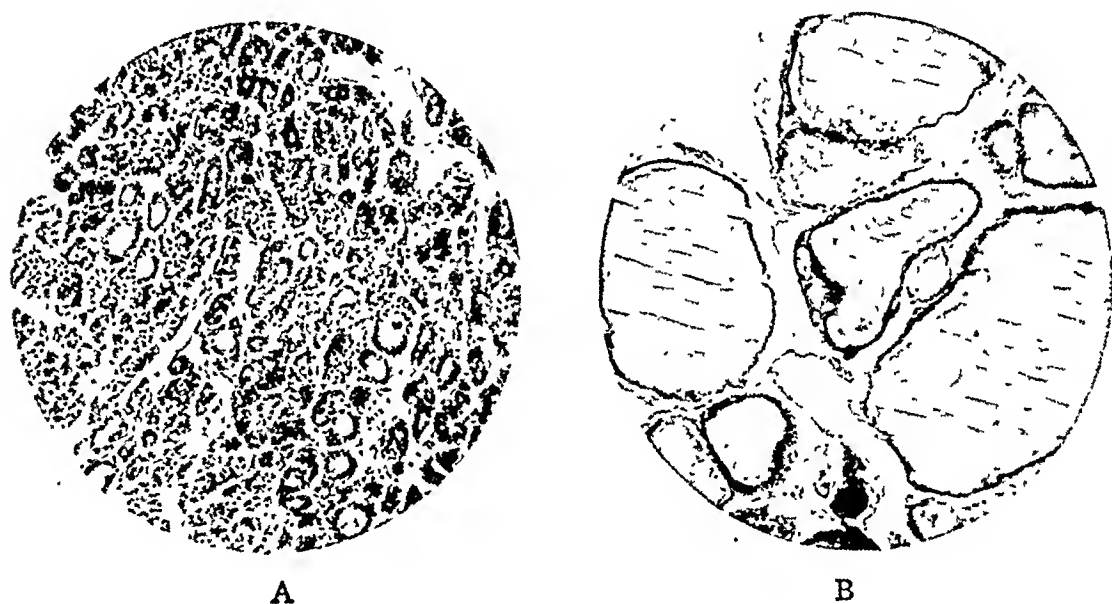


FIG. 1.—(A) Fetal adenoma of thyroid. Note that the follicles are principally tubular in type but some are microfollicular. ($\times 150$)

(B) Paranodular thyroid tissue. Diffuse colloid goiter of adolescence. Note the large size of the follicles and the presence of proliferative changes. ($\times 150$)

small in a few instances and macrofollicular in other areas, but principally tubular in type and the interstitial tissue was small in amount. The tissue surrounding the nodule (Fig. 1B) showed the acini larger than normal and the cells flattened. The colloid was moderately dense and showed very little vacuolation. However, a few areas of hyperplasia consisting of heightening of the cells with layering and plication, were noted here and there throughout the paranodular tissue. *Final Diagnosis:* Diffuse nontoxic colloid goiter with a single fetal adenoma.

The postoperative condition remained excellent. The temperature, pulse and respirations remained normal. The patient was kept in semi-Fowler's position and an ice collar was applied over the dressing. Sips of water were allowed as desired, and food as soon as it could be taken. There was never evidence of parathyroid deficiency or of recurrent laryngeal nerve injury. The wound healed well. Alternate sutures were removed on the second and the remainder on the fourth day. The patient was discharged on the fourth

day, June 27, 1944, as improved. One tablet of oridine (iodine 10 mg.) once daily for 70 days was prescribed.

She was seen in the Out-patient Surgical Clinic on September 11, 1944, at which time she was well and the wound appeared healed and in good condition. She had taken one tablet of oridine (10 mg. of iodine) daily for 70 days. The thyroid, on June 25, 1945, was normal in size and consistency, and the basal metabolic rate was plus one per cent. The patient was then considered cured.

COMMENT.—Twenty hours intervened between the administration of the radioiodine solution and the thyroidectomy. Study of this goiter revealed remarkable differences between the storage of iodine by the fetal adenoma (Fig. 1A) and that by the typical nontoxic diffuse colloid goiter (Fig. 1B) which surrounded the adenoma. The adenoma (Fig. 2 M. H.) contained a

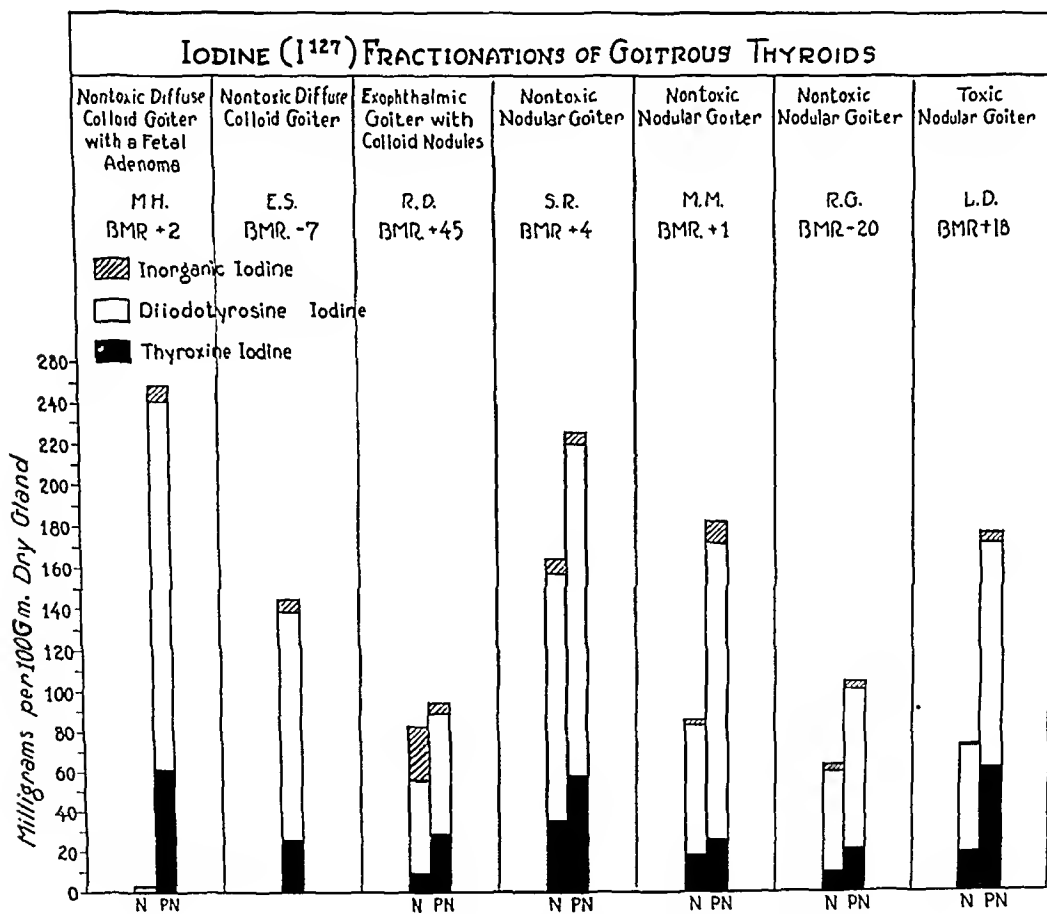


FIG. 2.—N—Nodular thyroid tissue, PN—Paranodular thyroid tissue.

minimum of elemental iodine, 2.7 milligrams per 100 Gm. of the dried gland, of which 1.6 mg. per cent was distributed in the diiodotyrosine fraction, 0.9 mg. per cent in the thyroxine fraction, and 0.4 mg. per cent in the inorganic fraction. This was much less than the figures for the paranodular tissue (Fig. 2 M. H.) which contained 250.0 mg. per cent of elemental iodine I^{127} per 100 Gm. of dried gland of which the diiodotyrosine fraction was largest, 179.0 mg.

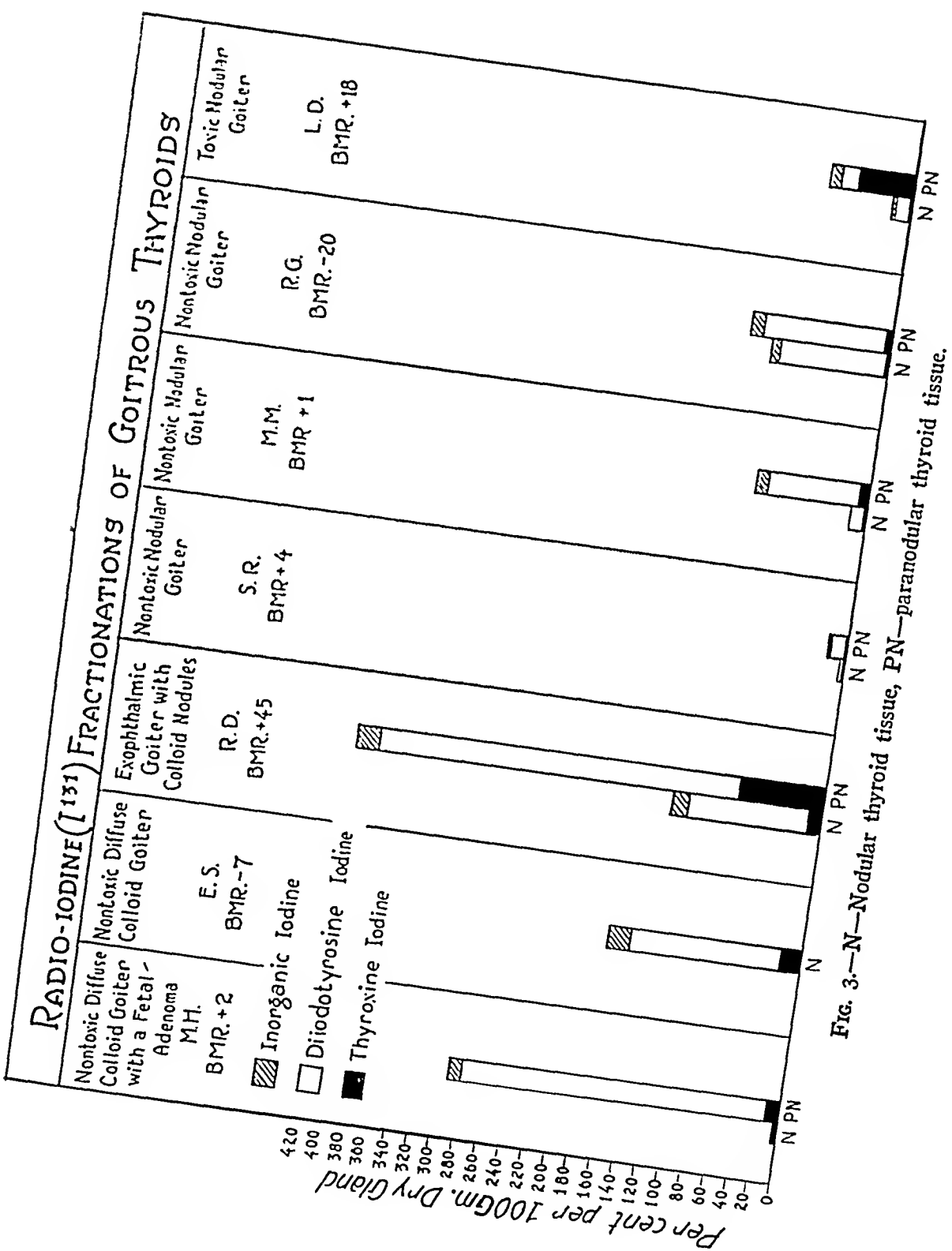


Fig. 3.—N—Nodular thyroid tissue, PN—paranodular thyroid tissue.

per cent, the thyroxine fraction being 63.3 mg. per cent and the inorganic fraction 7.6 mg. per cent.

The nodule (Fig. 3 M. H.) contained a minimum of the radioiodine given 20 hours before thyroidectomy, 2.4 per cent per 100 Gm. of dry gland, of which 1.5 per cent was distributed in the inorganic iodine fraction, 0.9 per cent in the diiodotyrosine and 0.6 per cent in the thyroxine fraction. These figures reveal much less avidity for radioiodine by the fetal adenoma than by the diffuse colloid goiter of adolescence (Fig. 3 M. H.) which contained 195.2 per cent of the radioiodine given per 100 Gm. of dry gland, of which the diiodotyrosine fraction was largest, 267.2 per cent, the thyroxine fraction being 12.9 per cent and the inorganic fraction 8.3 per cent.

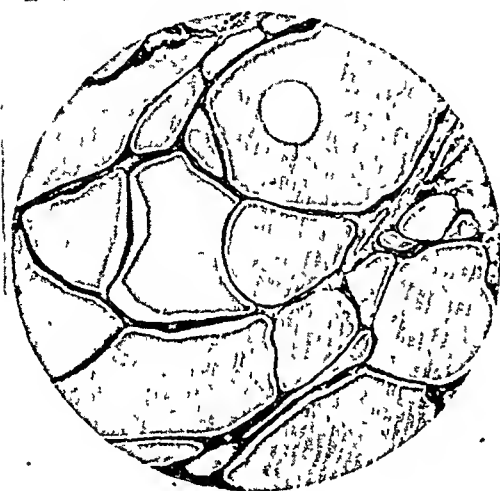


FIG. 4.—Diffuse colloid goiter. The lining epithelium is much flattened, and the colloid is dense and abundant. ($\times 150$)

These figures also demonstrate that the diffuse colloid goiter of adolescence produced much more of the physiologically active organic iodine compounds (thyroxine and diiodotyrosine) than the fetal adenoma which produced minimal amounts.

Protocol of E. S.—No. 445276, with Nontoxic Diffuse Colloid Goiter: E. S., a married colored female, age 27, entered University Hospital, June 20, 1944, for the surgical treatment of goiter.

She first became aware of goiter about three years ago. Except for occasional dysphagia and dyspnea it remained symptomless. The past history was negative except for sickle cell anemia.

Physical examination revealed a well-nourished, colored female, who was quiet. The thyroid was diffusely, symmetrically and moderately enlarged.

Admission red blood count was 5,270,000, with the hemoglobin 14.5 Gm. per cent. There was slight sickling of the red cells. The white blood count was 8,950, with the neutrophils 49 per cent, lymphocytes 46 per cent, monocytes 4 per cent, and eosinophils 1 per cent. The urinalysis was negative. The blood Wassermann and Mazzini tests were negative. The average basal metabolic rate was minus 7 per cent, with the basal pulse 80, respirations 19, temperature 98.2°F., the blood pressure 128/72, and the weight 120 pounds. The total blood iodine averaged 2.70 and the acetone-insoluble fraction 1.02 micrograms per cent, which are normal. The blood urea nitrogen was 13 mg. per cent. Renal function tests were normal. The blood prothrombin was 65 per cent, which is normal. The blood cholesterol was 316 mg. per cent. Roentgenography revealed the trachea displaced to the left.

Radioactive iodine was given in grape juice on July 17, 1944, at 12 noon. No other iodine was given at any time preoperatively.

Bilateral subtotal thyroidectomy was done by one of us (I. D. P.) under avertin, cyclopropane, oxygen and helium anesthesia at 8 A.M. on July 18, 1944. It was followed by an uneventful recovery.

The goiter as removed weighed 59 Gm. About 15 Gm. of thyroid tissue were left

behind. The right thyroid lobe as removed measured $6.5 \times 3.5 \times 4$ cm. The left lobe measured $8 \times 3 \times 3$ cm. The isthmus measured $3 \times 4 \times 2$ cm., and the pyramidal lobe measured 1.5 cm. in diameter. The goiter grossly appeared symmetrically and generally enlarged. An excess amount of colloid was noted on cut-section. Microscopically (Fig. 4), the acini were much larger than normal, the cells were flattened and the colloid was abundant and moderately dense, with few vacuoles. However, a few areas of spur formation were also noted. *Final Surgical Diagnosis:* Nontoxic diffuse colloid goiter.

COMMENT.—There was a 20-hour interval between administration of the radioiodine and the thyroidectomy. This goiter, which was typically diffuse colloid in character (Fig. 4) and nontoxic, contained 163 mg. per cent of elemental iodine I^{127} , of which the diiodotyrosine fraction was largest, 114 mg. per cent, with the thyroxine 25 mg. per cent and the inorganic fraction 3.5 mg. per cent (Fig. 2 E. S.). It showed considerable avidity for radioiodine (Fig. 3 E. S.) comparable to the nontoxic diffuse colloid goiter of adolescence (M. H.) storing 163 per cent per 100 Gm. of dry gland of the radioiodine given 20 hours prior to thyroidectomy. The diiodotyrosine fraction was largest, 137 per cent, the thyroxine fraction being 16 per cent and the inorganic fraction 13 per cent.

This study again demonstrates the increased avidity for iodine (Fig. 3 E. S.) by the nontoxic diffuse colloid goiter and its ability to produce large percentages of physiologically active organic iodine compounds.

Protocol of R. D.—No. 446794, with Exophthalmic Goiter and Three Small Colloid Nodules, Treated Preoperatively without Iodine or Thiouracil: R. D., a colored female, age 39, was admitted to University Hospital, August 1, 1944, for the surgical treatment of exophthalmic goiter.

She had been well up to January, 1944, when severe nervousness occurred. This was accompanied by easy fatigability, muscular weakness, emotional and heat instability, palpitation, exophthalmos, a gradually enlarging goiter and loss of body weight from 142 to 133 pounds in spite of a voracious appetite.

Physical examination revealed a well-developed woman who appeared to have lost weight recently. The facial expression was of frozen terror. Exophthalmometric readings were 20 mm. bilaterally. The thyroid was moderately and diffusely enlarged. There was fine tremor of the extended hands.

Admission red blood count was 4,500,000, with the hemoglobin 13.2 Gm. per cent, and the white blood count 8,300, with the neutrophils 66 per cent, lymphocytes 31 per cent, monocytes 2 per cent and eosinophils 1 per cent. The urinalysis was negative. The blood Wassermann and Mazzini tests for syphilis were negative. The prothrombin was 75 per cent, which is normal. The hippuric acid test of liver function yielded 2.97 Gm. The total blood iodine averaged 18.63 and the acetone insoluble fraction 11.11 micrograms per cent, which are greatly increased.

The basal metabolic rate was plus 45 per cent on August 2, 1944, with the basal pulse 96, respirations 23, temperature 98.6°F. ; the blood pressure 118/76; and the weight 138 pounds. The patient was prepared in the usual manner for operation except that iodine was omitted. A high caloric, high carbohydrate, high protein, high mineral and high vitamin diet was given. Extra calcium and phosphorus as well as vitamin D were given as two calirad wafers (dicalcium phosphate with viosterol) three times daily. Two capsules of vitamin B complex three times daily, ten milligrams of thiamin chloride three times daily and synkayvite (synthetic vitamin K) were given. Sufficient bed rest was allowed. Adequate sedation with phenobarbital was used. With these methods¹⁸ alone, without use of iodine, the basal metabolic rate decreased to plus 27 per cent on August

14, 1944, with the basal pulse 80; respirations 18; temperature 98°F.; blood pressure 118/74; and the body weight 133 pounds.

Radioactive iodine was given in grape juice on August 14, 1944 at 5:30 P.M. No other iodine was given preoperatively.

Bilateral subtotal thyroidectomy under avertin, cyclopropane, ether, oxygen and helium anesthesia was done by one of us (I. D. P.) on August 15, 1944, at 8:30 A.M., and the postoperative course remained entirely uneventful.

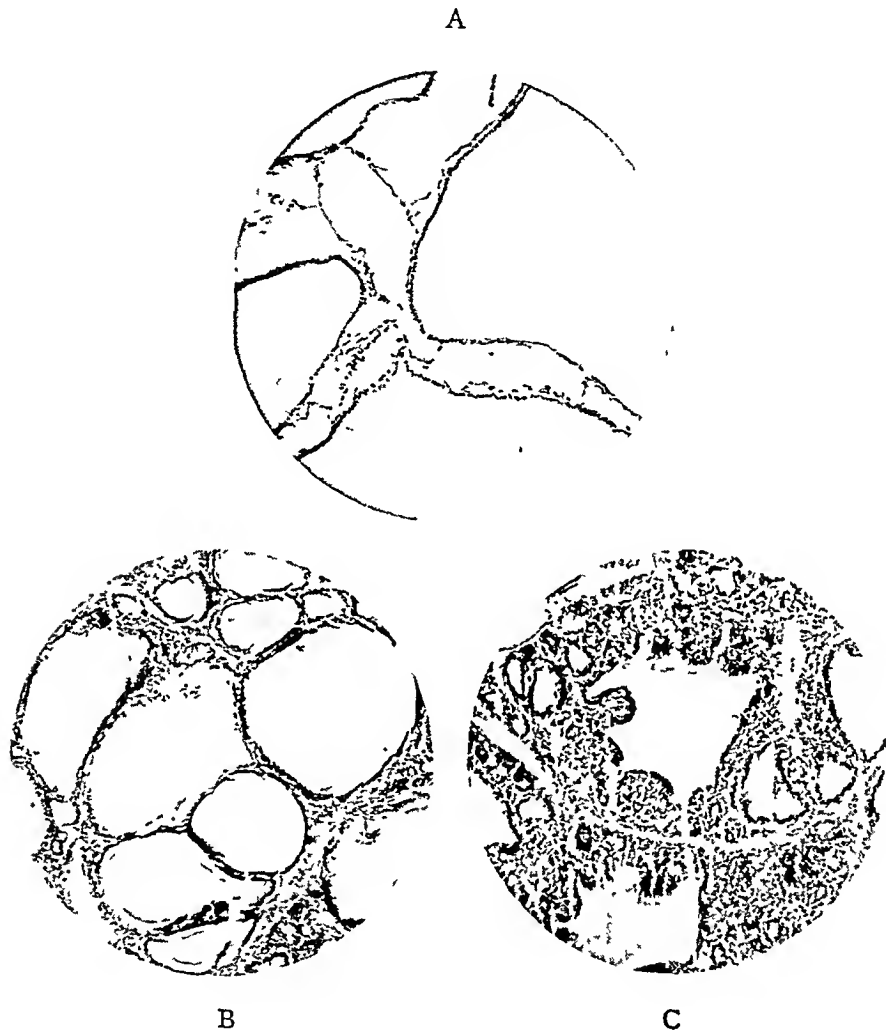


FIG. 5.—(A) Typical colloid nodule. ($\times 150$)

(B) Paranodular tissue. There were frequent areas of involution of this exophthalmic goiter gland even though the patient did not receive iodine in the preoperative preparation. ($\times 150$)

(C) Exophthalmic goiter. Much of the goiter consisted of this tissue. Note the tall cells, papillae and vacuoles. ($\times 150$)

The goiter as removed weighed 46 Gm. About 10 Gm. of thyroid were left behind. The right lobe measured $8 \times 3 \times 3$ cm. and weighed 20 Gm. The left lobe and isthmus measured $6.5 \times 4 \times 3$ cm., and weighed 26 Gm. On gross observation the gland appeared diffusely and symmetrically enlarged except for a small cyst containing straw-colored fluid and a small nodule which was observed in the lower pole of the right lobe. The cystic fluid was aspirated for study. On cross-section, the nodule of the right lobe meas-

ured one centimeter in diameter. Cross-section also revealed two small nodules in the lower pole of the left lobe. Each measured about 8 mm. in diameter. The gland otherwise appeared beefy in character and contained a minimum of colloid. The nodule studied was typically colloid in type (Fig. 5A). The paranodular tissue showed areas of hyperplastic tissue characteristic of exophthalmic goiter (Fig. 5C) as well as frequent areas of involution (Fig. 5B).

COMMENT.—The interim between radioiodine administration and thyroidectomy was 15 hours. This patient with exophthalmic goiter received no preoperative iodination and the biochemical findings are most remarkable.^{17b} The paranodular tissue which was typical diffuse hyperplastic goiter (Fig. 5B) with not rare areas of involution (Fig. 5C) showed the least concentration (Fig. 2 R. D.) of elemental iodine I^{127} , 93.96 mg. per cent, of all paranodular tissues studied, and yet its avidity (Fig. 3 R. D.) for radioiodine was tremendous, 410.14 per cent per 100 Gm. of dry thyroid gland, and unsurpassed by any of the thyroid tissues studied. Even though this paranodular tissue (Fig. 2 R. D.) contained small amounts of physiologically active elemental organic iodine compounds, 60.9 mg. per cent diiodotyrosine and 26.9 mg. per cent thyroxine, with the inorganic fraction 6.16 mg. per cent, the markedly increased ability to produce these physiologically active organic iodine compounds (Fig. 3 R. D.) was presented by the high values for the diiodotyrosine radioiodine I^{131} of 313.0 per cent and 76.6 per cent for the thyroxine fraction. The inorganic iodine I^{131} was 20.44 mg. per cent.

The nodular tissue which was typically colloid (Fig. 5A) in character and which was probably only incidentally present also presented significant findings. Its ordinary iodine I^{127} content was smaller (Fig. 2 R. D.) than that of the paranodular tissue, 81.12 mg. per cent, with the diiodotyrosine fraction 45.6 mg. per cent, the inorganic fraction 26.29 mg. per cent and the thyroxine fraction 9.23 mg. per cent. Its avidity for radioiodine (Fig. 3 R. D.) was much greater, 128.55 per cent, than that of the usual nodule, and yet remarkably less than that of the diffuse hyperplastic tissue of exophthalmic goiter, 410.14 per cent. Its ability to produce physiologically active iodine compounds (Fig. 3 R. D.) was also less than that of the paranodular tissue so that the diiodotyrosine was 108.4 per cent, with the thyroxine fraction 10.69 per cent, the inorganic fraction being 9.46 per cent.

Protocol of S. R.—No. 446693, with Nontoxic Nodular Goiter: S. R., a colored housewife, age 54, was admitted to University Hospital, July 30, 1944, for surgical treatment of goiter.

She had had a goiter since the age of 7 years. There were no pressure or toxic symptoms. The goiter was nodular in character and her family physician advised thyroidectomy because of a fear of cancer.

Physical examination presented a well-developed and well-nourished female. A moderately large nodular goiter was present. Indirect laryngoscopy revealed paralysis of the left cord.

Admission red blood count was 4,500,000, with the hemoglobin 13 Gm. per cent. The white blood count was 5,000, with the neutrophils 66 per cent, lymphocytes 32 per cent and monocytes 2 per cent. The urinalysis was negative. The blood Wassermann and Mazzini tests for syphilis were negative. The basal metabolic rate determinations

averaged plus 4 per cent, with the basal pulse 80, respirations 18, temperature 98°F., blood pressure 126/70, and the weight 175 pounds. The total blood iodine averaged 5.82 and the acetone insoluble fraction 1.70 micrograms per cent. The blood urea nitrogen was 14.0 mg. per cent. The hippuric acid test of liver function yielded 3.13 Gm. Roentgenography revealed the trachea in normal position.

Radioiodine was given in grape juice on August 2, 1944, at 3:00 P.M.

Subtotal thyroidectomy was performed by one of us (I. D. P.) on August 3, 1944, at 9:00 A.M., under avertin, cyclopropane, oxygen and helium anesthesia. The postoperative course was uneventful.

The goiter as removed weighed 88 Gm. About 20 Gm. of thyroid tissue was left behind. The right thyroid lobe measured 6 x 3 x 4 cm. Cross-section revealed many colloid nodules, the largest of which measured 3 cm. in diameter. The left thyroid lobe and isthmus as removed measured 9.5 x 3.5 x 5.0 cm. It contained a multiplicity of

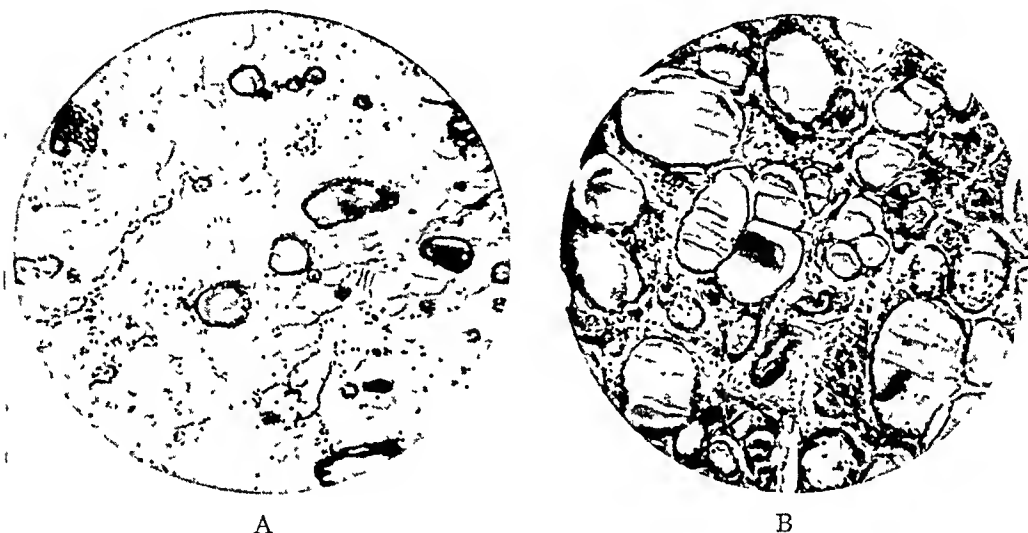


FIG. 6.—Nontoxic Nodular Goiter.

- (A) Nodule. Note that the small colloid-containing acini are widely separated by a peculiar material, the exact nature of which has not yet been determined. (x 150)
 (B) Paranodular tissue. Note the marked interacinar fibrosis and hyalinization and the tendency to accumulation of colloid over normal. (x 150)

nodules of varying size, the smallest measuring 5 mm. and the largest 3.5 cm. A pyramidal lobe which contained nodular tissue was also removed. All lobes revealed evidences of fibrosis, calcification, old hemorrhage, hyaline degeneration and cholesterol deposition. At each upper pole there was a moderate amount of thyroid tissue having a more normal appearance, but even this was the seat of degenerative changes. Microscopically, the nodules studied (Fig. 6A) showed the acini to be widely separated by a peculiar material, the exact nature of which has not been determined. The paranodular tissue (Fig. 6B) was the seat of marked interstitial fibrosis with hyalinization.

COMMENT.—Thyroidectomy was performed 18 hours subsequent to administration of the radioiodine. Both the nodular and paranodular tissues, even though presenting marked evidence of degenerative changes (Fig. 6A and B), revealed an abundance of elemental iodine (Fig. 2 S. R.), 160.2 and 228.0 mg. per cent, respectively, which may indicate that the patient had had iodine at home. Yet the nodular iodine remained lower and its fractions were 123.0 mg. per cent of diiodotyrosine, 34.6 mg. per cent of thyroxine, and 4.5 mg. per cent

of inorganic iodine. It is difficult to conceive that the small amount of colloid within the acini (Fig. 6A) could possibly store so much iodine. It is possible that the large amount of substance which separates the acini may be related to the colloid within the acini and may be able to store an increased amount of iodine. Diiodotyrosine was the largest of the paranodular iodine, 160.0 mg. per cent, the thyroxine fraction being 59.2 mg. per cent and the inorganic fraction 7.1 mg. per cent.

The avidity for radioiodine (Fig. 3 S. R.) was lower than that of all goiters studied, both for the nodular and paranodular tissues, 5.8 and 12.2 per cent, respectively. This may have resulted from decreased function due to the marked pathologic changes shown by both the nodular (Fig. 6A) and paranodular (Fig. 6B) tissues. On the other hand, it may indicate that the tissues had already been saturated by a former iodination at home, as is also indicated by the high inorganic iodine content of the blood.

Protocol of M. M.—No. 445877, with Nontoxic Nodular Goiter: M. M., a colored housewife, age 60, entered University Hospital, July 6, 1944, for the surgical treatment of goiter.

The patient had become aware of goiter 18 years ago. It remained symptomless up to about four years ago when she experienced dyspnea. Palpitation accompanied during the past few months.

Physical examination presented a tall, obese female in no apparent distress. A large multinodular goiter was easily palpable.

Admission red blood count was 4,520,000, with the hemoglobin 14 Gm. per cent. The white blood count was 7,650, with neutrophils 70 per cent, lymphocytes 26 per cent, monocytes 2 per cent and eosinophils 2 per cent. Urinalysis was negative. The blood Wassermann and Mazzini tests for syphilis were negative. The basal metabolic rate averaged plus 3 per cent with the basal pulse 64, respirations 9, temperature 98.4°F., blood pressure 155/88, and the weight 218 pounds. The total blood iodine was 5.45, and the acetone-insoluble fraction 1.92 micrograms per cent. The blood urea nitrogen was 14.0, and the blood sugar 80 mg. per cent. Phenolsulfonphthalein test of renal function yielded 40 per cent excretion of the dye during the first hour and 15 per cent during the second hour after intravenous administration. The hippuric acid test of liver function yielded 3.54 Gm., which is normal.

Radioactive iodine was given at 7:00 P.M. on July 7, 1944. Subtotal thyroidectomy was performed by one of us (I. D. P.) under avertin, cyclopropane and oxygen anesthesia at 12 noon on July 8, 1944. The postoperative reaction was minimal.

The goiter as removed weighed 206 Gm. It consisted principally of nodular tissue. The paranodular tissue was minimal. About 10 Gm. of thyroid tissue were left behind. The left thyroid lobe and isthmus as removed weighed 200 Gm. and measured 10 x 9 x 5.5 cm. It contained many nodules varying in size from 0.5 to 4 cm. in diameter. Cross-section showed many nodules which were principally colloid in nature but varied greatly in character because of varying degrees of fibrosis and hemorrhage. The nodules were well-circumscribed by fibrous connective tissue. Marked degenerative changes including fibrosis, calcification, hyalinization, cholesterolization and cyst formation were generally present. The right thyroid lobe as removed weighed 6 Gm. It measured 4 x 2 x 1.5 cm. This lobe contained two small nodules measuring 0.5 and 1.0 cm. in diameter, respectively. These were colloid in character. Microscopically, the tissue studied showed marked fibrosis, with hyalinization of the nodular portion (Fig. 7A). The paranodular tissue was more normal in appearance (Fig. 7B) but it also showed an increased stroma due to edema.

COMMENT.—Thyroidectomy was performed 17 hours subsequent to giving the radioactive iodine. The nodule, which was colloid in character (Fig. 7A), but presented much varied evidence of degeneration, contained (Fig. 2 M. M.) 86.9 mg. per cent of elemental iodine, of which the diiodotyrosine fraction was largest, 63.6 mg. per cent, the thyroxine fraction being 17.8 mg. per cent and the inorganic fraction 1.9 mg. per cent. The paranodular tissue, which was more normal in appearance (Fig. 7B) and yet showed an increased stroma, clearly demonstrated a greater content of ordinary iodine (Fig. 2 M. M.), 190.2 mg. per cent, the diiodotyrosine fraction being largest, 144.8 mg. per cent, with the thyroxine 25.9 mg. per cent and the inorganic fraction 9.5 mg. per cent.

The nodule (Fig. 3 M. M.) also showed less avidity for radioiodine than the paranodular tissue, 14.0 per cent, and less production of physiologically active organic iodine, with the diiodotyrosine 11.4 per cent and the thyroxine fraction 2.1 per cent, the inorganic fraction being 0.35 per cent. The paranodular tissue, on the other hand (Fig. 3 M. M.), retained 90.0 per cent per 100 Gm. of dry gland of the radioiodine ingested, the diiodotyrosine fraction being largest, 82.8 per cent, with the inorganic 11.1 per cent and the thyroxine 6.7 per cent.

Protocol of R. G.—No. 445841, with Nodular Goiter with Mild Hypothyroidism: R. G., a white, married female, age 44, entered University Hospital, July 6, 1944, for management of nontoxic nodular goiter. She first became aware of adolescent goiter at 17 years of age, which subsequently almost disappeared. Later it enlarged during each of 12 pregnancies and receded during the intervals. It gradually enlarged five years ago and since then it has remained large. Only an occasional choking sensation accompanied its presence up to about two years ago when she began to be troubled with excessive weakness and easy fatigability. Loss of appetite was associated.

Physical examination showed a well-developed and well-nourished white female. Examination of the neck revealed a large nodular goiter.

Admission red blood count was 4,250,000, with the hemoglobin 12.5 Gm. per cent. The white blood count was 8,500, with the neutrophils 56 per cent, lymphocytes 42 per cent, and basophils 2 per cent. The urinalysis was negative. The average basal metabolic rate determination was minus 20 per cent, with the basal pulse 72, the respirations 10, the temperature 98°F., blood pressure 120/70, and the weight 141 pounds. The total blood iodine averaged 3.13 and the acetone-insoluble fraction 1.07 micrograms per cent, which are normal. The blood urea nitrogen was 18.0, and the blood sugar was 85 mg. per cent. The serum cholesterol was 250, with the free fraction 63, and the ester 185 mg. per cent (75 per cent). The blood prothrombin was 125 per cent of the average normal value, while the hippuric acid liver function test yielded 2.82 Gm., which is normal. The sedimentation rate was 17 mm. in one hour, which is normal. Roentgenography of the chest and neck revealed a left lateral deviation of the trachea.

Radioactive iodine was given in grape juice on July 24, 1944, about 40 hours before operation. Bilateral subtotal thyroidectomy was performed by one of us (I. D. P.) under avertin, cyclopropane, oxygen and helium anesthesia at 8:00 A.M. on July 26, 1944. The postoperative course remained generally uneventful.

The goiter as removed weighed 176 Gm. About 20 Gm. of thyroid tissue were left behind. The left lobe measured 11 x 3.5 x 5.5 cm. and the right lobe with the isthmus measured 11.5 x 3.5 x 6 cm. The goiter was grossly nodular and presented on cross-section many nodules of varying size, the smallest measuring 5 mm. and the largest 2.5 cm. in diameter. Most of the nodules were colloid in type and not completely circumscribed.

BEHAVIOR OF THYROID NODULES

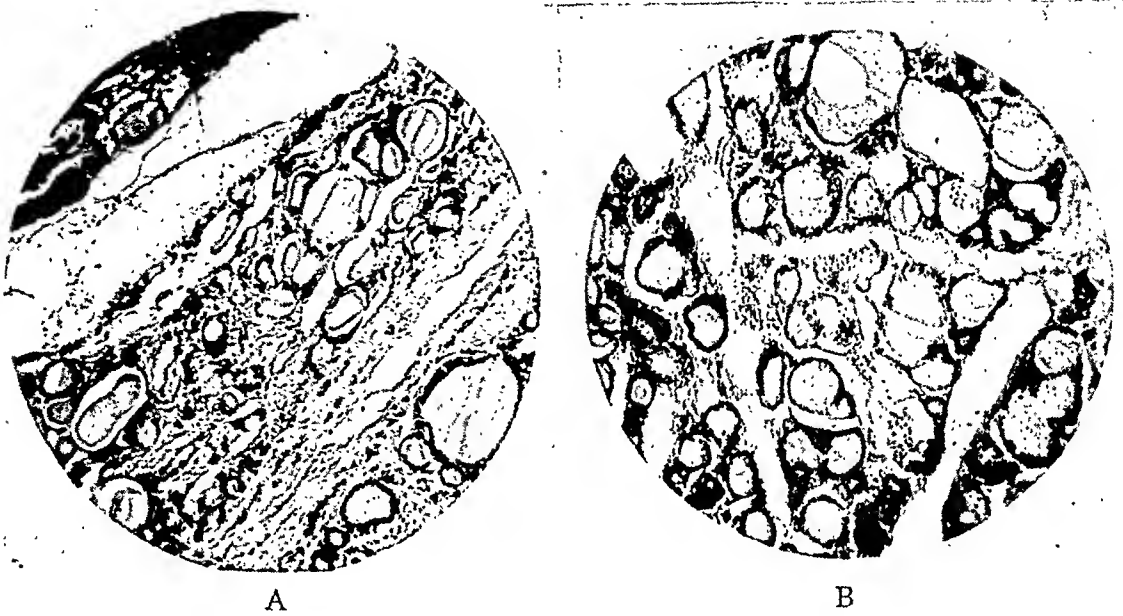


FIG. 7.—Nontoxic Nodular Goiter.

- (A) Nodule. Note the marked fibrosis, hyalinization and edema. The amount of acinar tissue is markedly decreased. (x 150)
(B) Paranodular tissue. This is more normal in appearance but shows stromal edema and a tendency to accumulation of colloid over normal. (x 150)

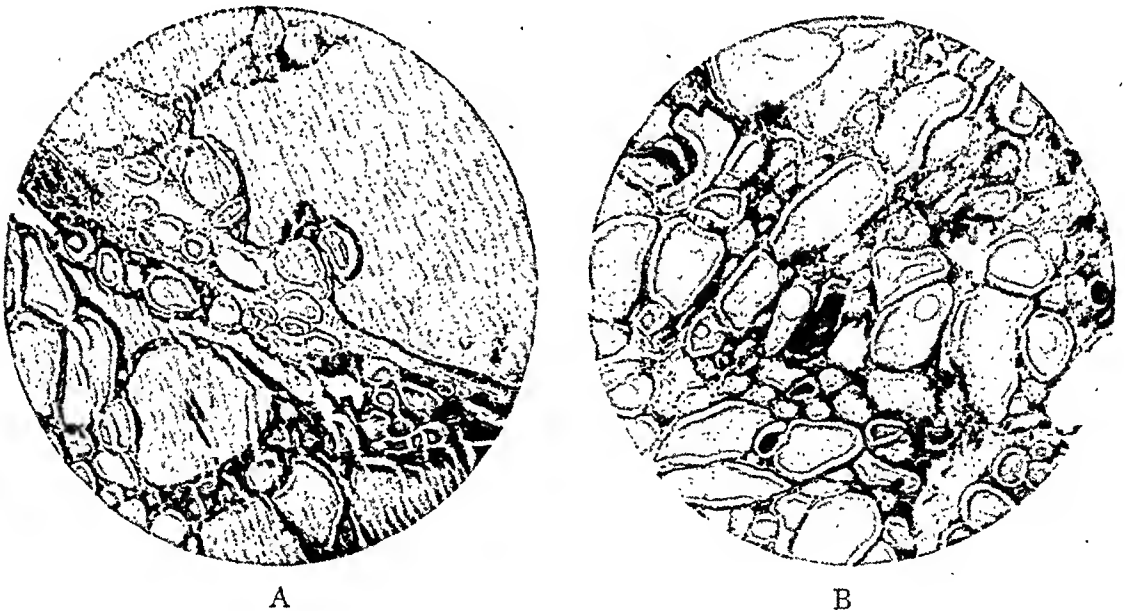


FIG. 8.—Nontoxic Nodular Goiter.

- (A) Colloid nodule. The nodule is typically colloid in character and shows formation of follicles of enormous size filled with much colloid. There are also areas of hyperplasia with plication. (x 150)
(B) Paranodular tissue. This tissue shows stromal fibrosis and hyalinization with a tendency to increased colloid accumulation suggestive of colloid goiter. (x 150)

Grossly, these appeared much like the surrounding tissue. Evidences of fibrosis, fatty degeneration and old hemorrhage were present. Nodular tissue was moderate in amount while the paranodular tissue was abundant and practically all located in the upper pole and posterior areas. The paranodular tissue also showed moderate fibrosis. Microscopically (Fig. 8), the nodular and paranodular tissue studied showed similar degenerative changes and differed in that the nodule was typically colloid in character and showed a greater tendency to formation of follicles of enormous size with flattened epithelium and filled with much colloid, as well as few areas of hyperplasia. *Final Surgical Diagnosis:* Nontoxic nodular goiter.

COMMENT.—This patient was thyroidectomized about 40 hours subsequent to administration of radioiodine, the interval being about twice as long as for other patients investigated. The nodular tissue (Fig. 2 R. G.) contained 66.0 mg. per cent of the ordinary iodine I^{127} , of which 51.0 mg. per cent were distributed in the diiodotyrosine fraction, 9.2 mg. per cent in the thyroxine, and 2.4 mg. per cent in the inorganic fraction. The paranodular tissue (Fig. 2 R. G.) showed a definite increase in the retention of iodine over the nodular tissue. It contained 113.0 mg. per cent of iodine per 100 Gm. of the dry gland, of which the diiodotyrosine fraction was largest, 80.0 mg. per cent, the thyroxine fraction being 20.5 mg. per cent, and the inorganic fraction 2.6 mg. per cent.

Study of this goiter showed slightly less avidity for radioiodine by the nodular than by the paranodular tissue (Fig. 3 R. G.). Except for less avidity for iodine, the paranodular tissue simulated, to a greater extent, the fractional distribution of iodine in the nontoxic diffuse colloid goitrous tissue of M. H. and E. S. The nodular tissue stored 103.0 per cent per 100 Gm. of the dry gland of the radioiodine given 40 hours before thyroidectomy, of which 95.0 per cent were distributed in the diiodotyrosine fraction, 3.8 per cent in the thyroxine, and 3.6 per cent in the inorganic fraction. The paranodular tissue contained 124.0 per cent per 100 Gm. of the dry gland, of which 106.0 per cent was distributed in the diiodotyrosine fraction, 59 per cent in the thyroxine, and 4.6 per cent in the inorganic fraction.

It is not surprising that there is the least percentage difference in the avidity and fractional distribution of radioiodine between the nodular and paranodular tissue of this gland (Fig. 3 R. G.) when compared to other nodular goiters studied. As mentioned above, the nodules were colloid in type, appeared much like the surrounding tissue, and grossly were not completely separated from the paranodular tissue. Microscopically, the nodular (Fig. 8A) and paranodular (Fig. 8B) tissue studied also showed almost similar degenerative changes and differed only in that the nodule was typically colloid in character and showed more tendency to formation of follicles of enormous size as well as a few areas of hyperplasia.

Note also that the content of ordinary iodine is less and that the avidity for radioiodine by both the nodular and paranodular tissues of this goiter is greater than that of nontoxic nodular goiters of the other patients, which may indicate that the hypothyroidism here is due to an iodine deficiency. On the

other hand, the increase in storage of radioactive iodine may have been due to the longer interval between radioiodine administration and thyroidectomy.

Protocol of L. D.—No. 445388, with Mildly Toxic Nodular Goiter: L. D., a colored maid, age 56, was admitted to University Hospital on April 3, 1944, for surgical treatment of goiter.

She had had a goiter since the age of 16 years. This remained symptomless until recent years. About four years ago she experienced sweating, generalized nervousness, restlessness, palpitation and dyspnea. Severe headaches and occasional nausea and vomiting were associated. Loss of weight from 190 to 173 pounds had occurred during the past three weeks. She was a known diabetic for nine years, this being controlled by diet and insulin. Supravaginal hysterectomy had been performed in 1916.

Physical examination showed an obese colored female lying quietly in bed. A slightly nodular, moderately large bilateral goiter was palpable. The right was the larger.

Admission red blood count was 4,260,000, with the hemoglobin 16 Gm. per cent. The white blood count was 5,740, with the neutrophils 46 per cent, lymphocytes 41 per cent, monocytes 9 per cent and eosinophils 4 per cent. The urinalysis was negative. The blood Wassermann and Mazzini tests for syphilis were negative. The basal metabolic rate on April 4, 1944, was plus 17 per cent, with the basal pulse 88, respirations 17, temperature 98.2°F., blood pressure 172/100, and the weight 173 pounds. The total blood iodine was 4.82 on April 4, 1944, with the acetone-insoluble fraction 2.20 micrograms per cent. The blood urea nitrogen was 10, and blood sugar 121 mg. per cent. Phenolsulfonphthalein test of renal function showed 60 per cent excretion during the first hour and 5 per cent excretion during the second hour after intravenous injection. Blood cholesterol was 75.0 mg. per cent, which is low. Divided 24-hour urine specimens showed no sugar. Prothrombin was 57 per cent, which is low, and increased to 98 per cent after intramuscular synkayvite. Hippuric acid test of liver function was 2.5 Gm. per cent.

Because the patient developed an upper respiratory infection with acutely inflamed nasal and oropharyngeal mucosae, operation was postponed. She reentered University Hospital on June 23, 1944. During the interval the upper respiratory infection subsided. Preoperative therapy included rest, sedation, adequate control of the diabetes and a high calcium, phosphorus and vitamin intake. Iodine had been given up to May 25, 1944. The basal metabolic rate was plus 18 per cent on June 24, 1944, with the basal pulse 88, respirations 17, temperature 98.2°F., blood pressure 152/92, and the weight 172 pounds. The blood sugar was 157 mg. per cent. Divided 24-hour urine specimens showed practically no urinary sugar excretion.

Radioiodine was given orally in grape juice at 12:45 P.M. on June 25, 1944. Subtotal thyroidectomy was performed by one of us (I. D. P.) under avertin, cyclopropane, oxygen and helium anesthesia on June 26, 1944, at 11:45 A.M. During the postoperative course the diabetic status was carefully followed and the postoperative reaction remained minimal. She made an uneventful recovery. The diabetes, subsequently, could easily be controlled by diet, without insulin.

The goiter, as removed, weighed 118 Gm. It contained a moderate amount of nodular tissue. About 15 Gm. of fairly normal-appearing thyroid tissue were left behind. The right lobe measured 9 x 5 x 2.5 cm. It contained numerous nodules of varying size, the largest measuring 2 cm. in diameter. There was also present a considerable amount of paranodular thyroid tissue containing a moderate amount of colloid. The nodules were colloid in character and definitely circumscribed. Various degenerative changes including fibrosis, old hemorrhage and small cyst formations were present to a slight extent. The amount of paranodular definitely exceeded the nodular tissue. The left lobe measured 10.5 x 5 x 2.5 cm. and showed pathologic changes quite similar to the right lobe but contained much more diffuse paranodular colloid tissue and fewer colloid nodules. The isthmus measured 6 x 3.5 x 2 cm. Its appearance on cross-section was that of the left lobe. It contained one calcified nodule. Microscopically, the nodule studied (Fig. 9A) was

typically colloid in type. The mild hyperplasia, increase in height of the epithelial cells and the marked vacuolation are believed by some pathologists to represent considerable hyperactivity. The paranodular tissue (Fig. 9B) showed areas of involution.

COMMENT.—There was a delay of 23 hours between radioiodine administration and thyroidectomy. The nodules were definitely circumscribed by fibrous connective tissue which may explain the lower content (Fig. 2 L. D.), of elemental iodine I^{127} , 77.0 mg. per cent, of the nodular than of the paranodular tis-

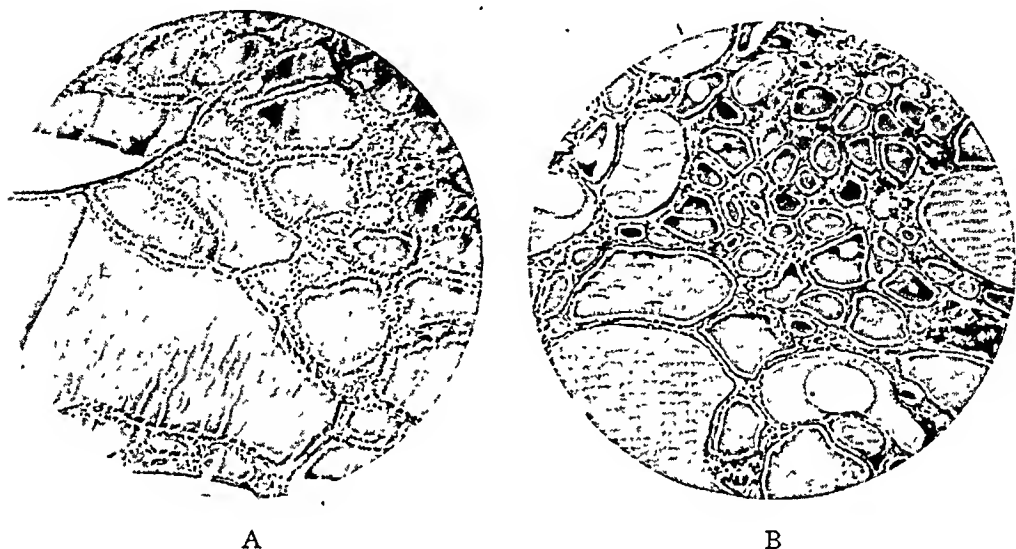


FIG. 9.—Toxic Nodular Goiter.

(A) Typical colloid nodule ($\times 150$). The mild hyperplasia, the increase in height of the epithelial cells and the marked vacuolation are said to indicate considerable activity.

(B) Paranodular tissue. ($\times 150$). This tissue is more normal in appearance but also shows flattened epithelium and large follicle formation suggestive of colloid goiter.

sue, 180.2 mg. per cent. Diiodotyrosine constituted the largest nodular iodine fraction, 63.2 mg. per cent, the thyroxine iodine being 10.0 mg. per cent and the inorganic fraction 1.0 mg. per cent. The paranodular elemental iodine fractions consisted of 108.2 mg. per cent diiodotyrosine, with thyroxine 63.3 mg. per cent and the inorganic fraction 3.5 mg. per cent.

The nodule also developed an avidity for radioiodine (Fig. 3 L. D.) of 16.5 per cent, which is much less than the 92.1 per cent of the paranodular tissue (Fig. 3 L. D.). The nodular diiodotyrosine iodine was 11.0 per cent, with the inorganic fraction 3.0 per cent and the thyroxine iodine 2.1 per cent. On the other hand, the paranodular tissue (Fig. 3 L. D.) showed remarkable production of 50.9 per cent of thyroxine iodine which is much greater than the 2.1 per cent of the nodular tissue and the 8.5 per cent of the paranodular tissue of the nontoxic goiters. This would indicate that the paranodular tissue is here responsible for the hyperthyroidism. The diiodotyrosine radioiodine was 15.8 per cent and the inorganic fraction 7.6 per cent.

DISCUSSION.—A surgicopathologic study was made of the nodules of six patients with various clinical types of thyroid disease and varying degrees of

toxicity. This study showed wide variations in their histologic picture from a colloid nodule, which is highly differentiated, to a true fetal adenoma, with little degree of differentiation. The nodules of the patients with toxic nodular and exophthalmic goiter were of the hyperplasia-involution type and not so-called true adenoma in type. Even though the nodules varied greatly microscopically, it is significant that the intensity of their activity was quite independent of the gland function. The nodules produced considerably less amounts of physiologically-active organic iodine compounds than the surrounding thyroid tissues, as indicated by the ordinary iodine I^{127} (Fig. 10) and radioiodine I^{131}

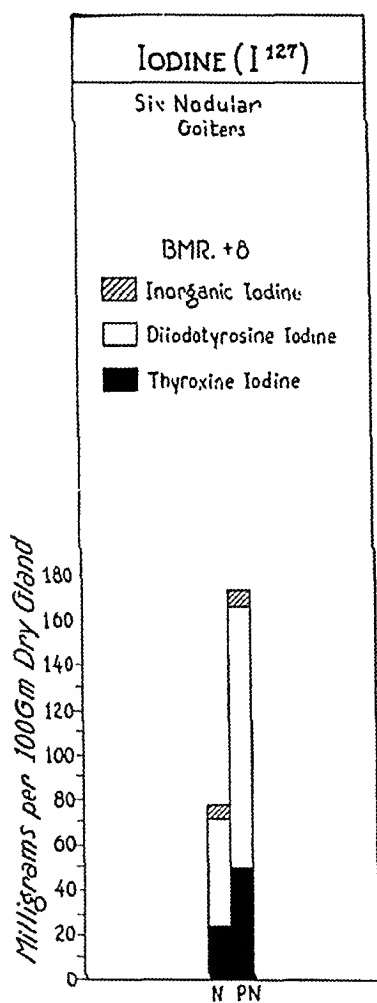


FIG. 10.—N—Nodular thyroid tissue, PN—Paranodular thyroid tissue.

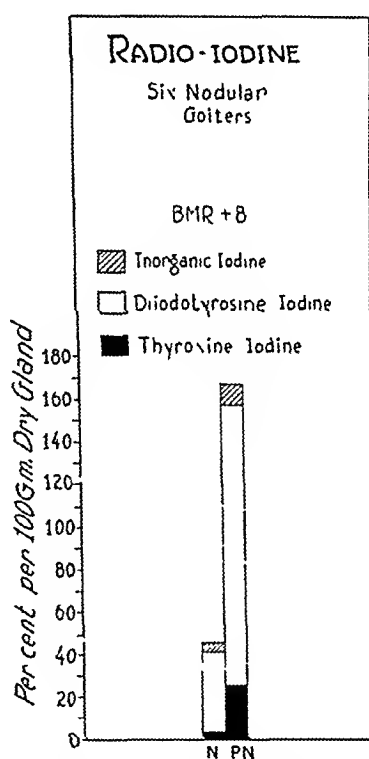


FIG. 11.—N—Nodular thyroid tissue, PN—Paranodular thyroid tissue.

(Fig. 11) fractionation studies.¹⁷ The ordinary iodine data confirms the work of Marine.¹⁴ None of the nodules studied could be considered so-called hyperfunctioning adenomas. These studies also indicated that some nodules, such as the fetal adenoma, contributed very little to the total thyroid function.

The nodules of the patients with toxic nodular and exophthalmic goiter studied also appeared functionally autonomous, since much less thyroid hormone was made by them than by the surrounding thyroid tissue. In the two hyperthyroid patients studied, the thyroxine-making activity was 7 and 25

times greater in the paranodular tissue over that of the corresponding nodules. The diiodotyrosine- and thyroxine-making activity of the nodules of the toxic nodular goiter patient appeared no different than that of the nodules of the nontoxic nodular goiter patients. One of the three small nodules of the exophthalmic goiter patient was studied and showed a slightly increased activity over that of the nodules of nodular goiter. This evidence suggests that the hyperactivity of the thyroid gland of the patients studied with toxic goiter does not arise from the nodules and that they are functionally incidental lesions.

The diffuse colloid tissue of two nontoxic goiters (M. H. and E. S.) revealed an increased avidity for radioiodine which exceeded that of the patient with toxic nodular goiter and approached that of the diffuse hyperplastic tissue of exophthalmic goiter (R. D.). However, the thyroxine-producing activity of the paranodular thyroid tissue of the patients with toxic nodular goiter and with exophthalmic goiter greatly exceeded the thyroxine-producing activity of all other forms of nontoxic pathologic thyroid tissue studied. It was 4.5 times greater than the thyroxine-producing activity of the diffuse colloid tissue and 5 times greater than that of its own nodules. It averaged 29 times greater than the activity of the nodular tissue and 7.5 times greater than the thyroxine-making activity of the paranodular tissue of three patients with nontoxic nodular goiter. The paranodular tissue showed least thyroxine-making activity in a patient (R. G.) with nodular goiter and hypothyroidism.

In previous studies^{21, 22} we pointed out that in exophthalmic goiter, even in the presence of continued excessive loss of iodine and a decreased content of thyroid iodine, the diffuse hyperplastic thyroid gland retained a greater than normal avidity for this element. Radioactive iodine studies again emphasize the great avidity for iodine shown by the diffuse hyperplastic gland of Graves' disease and also point out that the ability of the gland for thyroxine and diiodotyrosine formation is greatly increased. This signifies that the factor of thyroid constipation or increased storage of the thyroid hormone in the thyroid follicle is the probable cause of the beneficial effects of iodine therapy in hyperthyroidism.

We have often wondered why surgeons can even remove several hundred grams of adenomatous tissue from the patient with nontoxic nodular goiter, leaving behind only a few grams of the diffuse paranodular tissue and still without producing an appreciable change in the thyroid function or in the basal rate of metabolism. Why is it that similar large amounts of adenomatous tissue can be removed from the patient with toxic nodular goiter without producing postoperative hypothyroidism? These studies indicate that often the adenomatous tissue contributes little to the total thyroid function which no doubt explains the good surgical therapeutic end-results obtained in the usual case of toxic or nontoxic nodular goiter.

Our small series of cases indicates that the surgeon doing nodular goiter surgery should also be concerned with the amount of paranodular tissue to preserve. This, in order to save the optimum thyroid function for the patient. The diffuse paranodular tissue of all cases of nodular goiter (Figs. 1B, 6B, 7B, 8B and 9B) studied, presented many of the microscopic characteristics of

diffuse colloid goiter. The diffuse paranodular tissue of nontoxic nodular goiter and of nodular goiter with hypothyroidism acted biochemically to a greater extent, like the tissue of nontoxic diffuse colloid goiter (Figs. 12 and 13), which suggests that during thyroidectomy it is this tissue which should be conserved to protect the patient against further decrease in the function of the thyroid gland. Iodine, as well as desiccated thyroid when needed, should be given the patient postoperatively to help restore the remaining tissue to as normal as possible, for the same reason that iodine is given to the patient with adolescent goiter. On the other hand, in nodular goiter with hyperthyroidism the paranodular tissue acted biochemically to a greater extent, like the tissue of exophthalmic goiter (Figs. 12 and 13) and this tissue should be adequately resected to decrease the incidence of persistence or pseudorecurrence of the hyperthyroidism.

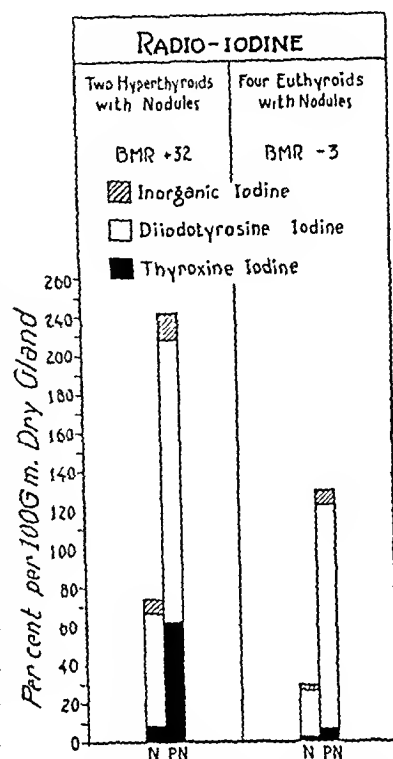


FIG. 12.—N—Nodular thyroid tissue, PN — Paranodular thyroid tissue.

Fortunately, in our experience, it frequently happens that the upper and posterior portions of the nodular gland (Figs. 14 and 15) are less affected by the degenerative processes, so that most of the paranodular tissue is located in this area and a reasonable margin of tissue free from adenomatous and cystic areas may be preserved in nontoxic nodular goiter (Fig. 16). It is almost invariably possible, also, to save a portion of the lower pole since this area does not share as often in the degenerative processes to the same extent as the lateral and anterior portions of the lobe. On the other hand, since the paranodular tissue is frequently similarly located near the danger zone (Figs. 14 and 15) even in patients with severe toxic nodular goiter when a more complete resection is indicated, the thyroidectomy must then be performed with added precaution. But by judicious planning of the plane of resection a large part of each lobe of the thyroid of the toxic nodular goiter patient can be excised (Fig. 16), when indicated, including especially the paranodular tissue and only fragments of thyroid tissue along with the recurrent laryngeal nerves and the parathyroid glands can be preserved at the sites already named.

The number of cases are too few to make far reaching conclusions and the data available at this time permit only a preliminary summary. They do indicate strongly that further studies in this direction should prove valuable. None of the patients who received tracer doses of radioiodine developed deleterious effects. All were followed carefully postoperatively for about one year and none developed evidences of hypometabolism. The basal metabolic rates on discharge from the Thyroid Clinic varied from minus 11 to plus 8 per cent, and all showed clinically a normal thyroid function.

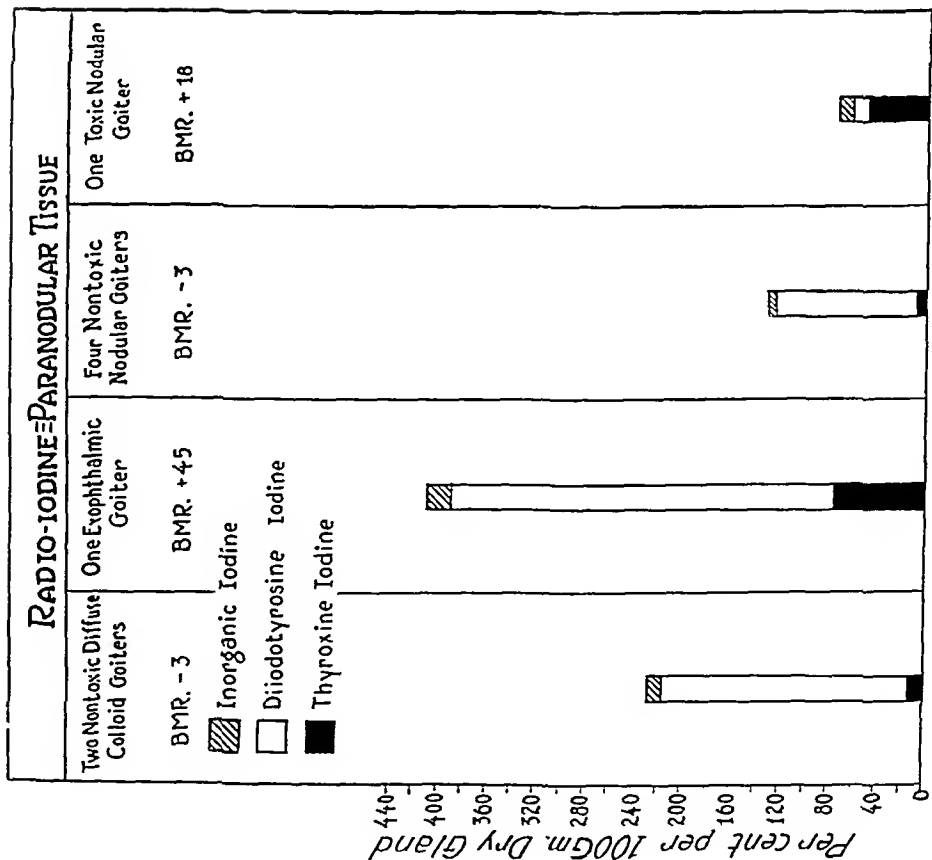


FIG. 13



FIG. 14.—Frequently the paranodular thyroid tissue (shaded) is located to a great extent in the upper pole area. The lower pole area may not share in nodulation.

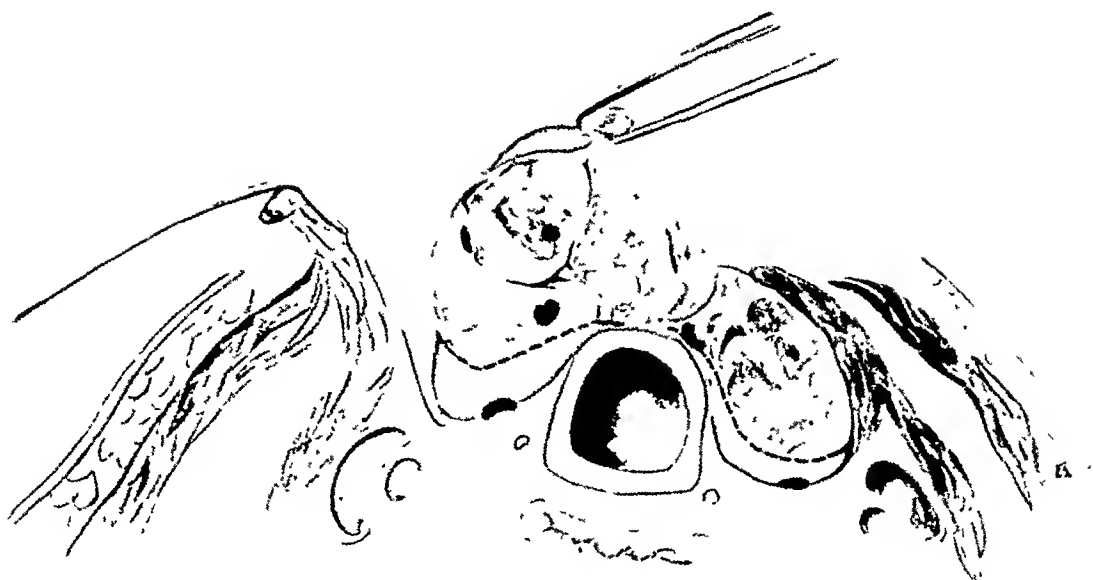


FIG. 15.—The posteromedial portion (shaded and demarcated by an interrupted line from the nodular goitrous tissue) of the thyroid gland not infrequently remains free of nodulation.

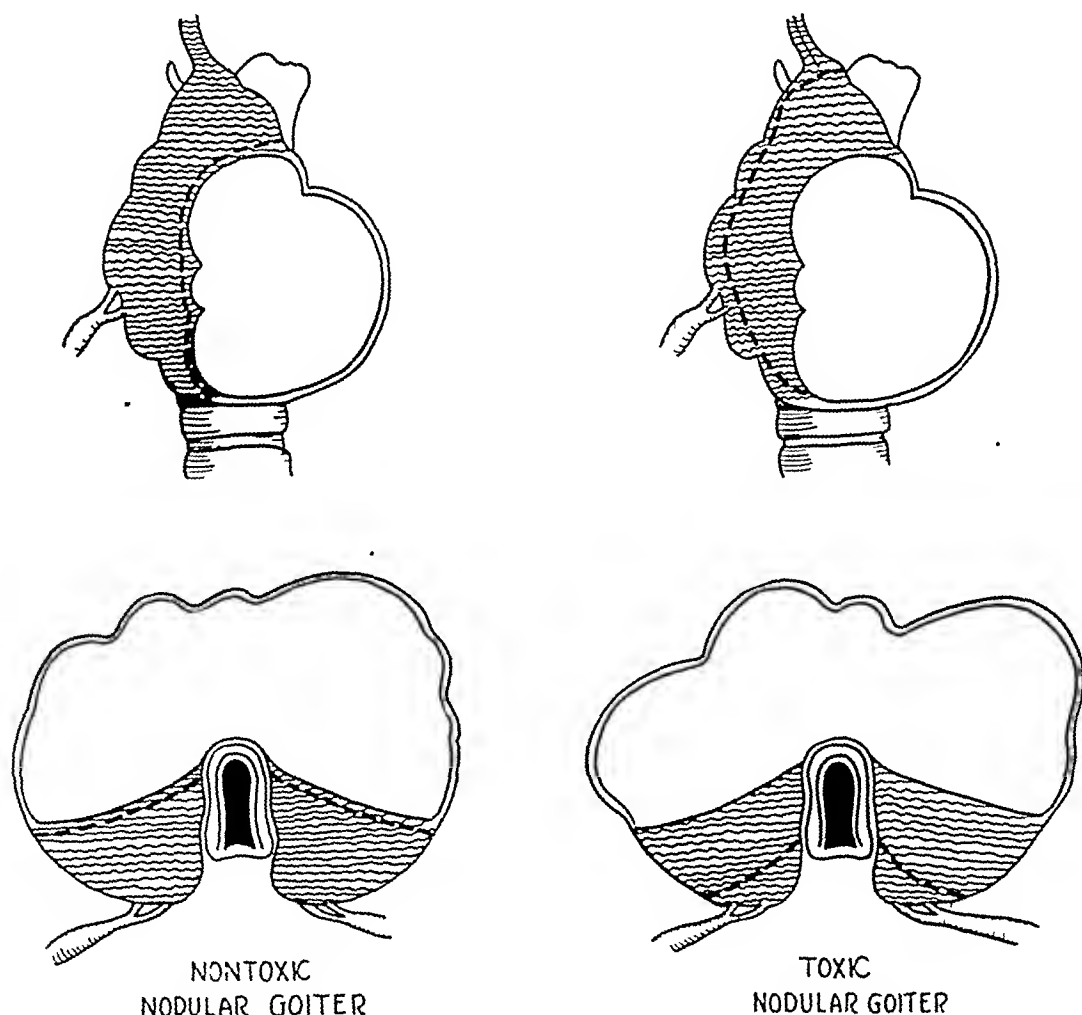


FIG. 16.—In nodular goiter surgery as much as possible of the paranodular tissue (shaded) should be conserved for the patient with nontoxic nodular goiter. The goitrous tissue should be more radically removed from the patient with toxic nodular goiter.

SUMMARY AND CONCLUSIONS

(1) Radioactive iodine and ordinary iodine fractionation as well as surgicopathologic studies were made of seven patients with various clinical types of thyroid disease and varying degrees of toxicity. The histologic pictures of the nodules of the six patients who had nodular goiter showed wide variations. The nodules of the patients with toxic nodular and exophthalmic goiter were of the hyperplasia-involution type and not so-called true adenoma in type. All nodules showed a decreased function when compared to the function of the corresponding paranodular thyroid tissues. The nodules of patients with nontoxic nodular goiter, toxic nodular goiter, exophthalmic goiter, and so-called fetal adenoma studied appeared functionally autonomous. They showed less avidity for administered radioiodine, and also much less thyroxine and diiodotyrosine was made by them than by the surrounding thyroid tissue.

(2) The diffuse goitrous tissue of two patients with nontoxic diffuse colloid goiter showed great avidity for iodine but its ability to produce thyroxine and diiodotyrosine did not appear greatly increased.

(3) The diffuse hyperplastic tissue of a patient with exophthalmic goiter showed the greatest avidity for iodine and the greatest ability to produce thyroxine and diiodotyrosine.

(4) The diffuse paranodular thyroid tissue of three patients with nontoxic nodular goiter, one having a mild hypothyroidism, showed many of the microscopic characteristics of diffuse colloid goiter. It acted biochemically to a greater extent like the tissue of nontoxic diffuse colloid goiter, which indicates that during thyroidectomy it is this tissue which should be left behind to protect the patient against further decrease in the function of the thyroid gland. Iodine should perhaps be given postoperatively to help restore the remaining tissue to as normal as possible.

(5) The paranodular thyroid tissue of a patient with toxic nodular goiter acted biochemically to a greater extent like the diffuse hyperplastic tissue of exophthalmic goiter, which suggested that this tissue should be more adequately resected to decrease the incidence of persistence or pseudorecurrence of symptoms.

REFERENCES

- ¹ Rienhoff, W. F.: Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter. *Arch. Surg.*, 13, 391, 1926.
- ² Kline, B. S.: The Origin of Adenomatous Goitre. *Am. J. Path.*, 1, 235, 1925.
- ³ Beck, B.: Über eingesackten Drüsengewebe—Kropf. *Arch. f. physiol. Heilk.*, 8, 136, 1849.
- ⁴ Wölfler, A.: Über die Entwicklung und den Bau des Kropfes. *Arch. f. klin. Chir.*, 29, 1, 1883.
- ⁵ Ribbert, H.: Das Adenom der Schilddrüse. *Frankfurt, Ztschr. f. path.*, 18, 55, 1915.
- ⁶ Virchow, R.: Die Krankhaften Geschwülste. Berlin, A. Hirschwald, 1863, vol. 13, No. 1, p. 15.
- ⁷ Hitzig, T.: Beiträge zur Histologie und Histogenese der Struma. *Arch. f. klin. Chir.*, 47, 464, 1894.

- ⁸ Michaud, L.: Die Histogenese der Struma nodosa. *Virchows Arch. f. path. Anat.*, 186, 423, 1906.
- ⁹ Murphy, W. B., and Ahnquist, G.: Origin of Fetal Adenoma in the Thyroid Gland. *Arch. Surg.*, 35, 211, 1937.
- ¹⁰ Boyd, William: *Surgical Pathology*, p. 185, W. B. Saunders Co., Phila., 1943.
- ¹¹ Johnson, J. R.: A Study of Nodular and Adenomatous Goiters with and without Hyperthyroidism: Thesis. Graduate School of the University of Minnesota, 1943, 57 pp.
- ¹² Parsons, W. B.: Adenoma of the Thyroid. *ANNALS OF SURGERY*, 85, 107, 1927.
- ¹³ Holst, J.: Bemerkungen zur pathologischen Physiologie der Strumen. I. Intern. Kropfkongr., Bern, 1927.
- ¹⁴ Marine, David: Benign Epithelial Tumors of the Thyroid Gland. *Jr. Med. Research*, 27, 229, 1912.
- ¹⁵ Wegelin, C.: The Thyroid. Special Edition of the Handbook of Special Pathological Anatomy and Histology, vol. 8, Julius Springer, Berlin, 1926.
- ¹⁶ Branovacky, Mileta: Die biologische Wirksamkeit verschiedener Kropfformen in Kaulquappenversuch. *Mitt. a.d. Grenzgeb. d. Med. u. Chir.*, 39, 563, 1926.
- ¹⁷ Leblond, C. P., Puppel, I. Darin, Riley, E., Radike, M., and Curtis, G. M.: (A) Radioiodine and Iodine Fractionation Studies of Human Goitrous Thyroids. *Jr. Biol. Chem.* In press; (B) Unpublished data.
- ¹⁸ Puppel, I. Darin, Gross, Harold T., McCormick, E. K., and Herdle, E.: The Rationale of Calcium, Phosphorus and Vitamin D. Therapy in Clinical Hyperthyroidism. *S. G. O.*, 81, 243, 1945.
- ¹⁹ Mann, W., Leblond, C. P., and Warren, S. L.: Iodine Metabolism of the Thyroid Gland. *Jr. Biol. Chem.*, 142, 905, 1942.
- ²⁰ Matthews, N. L., Curtis, G. M., and Brode, W. B.: The Determination of Iodine in Biological Materials. *Ind. and Eng. Chem., Anal. Ed.*, 10, 612, 1938.
- ²¹ Puppel, I. D., and Curtis, G. M.: Calcium and Iodine Metabolism in Thyroid Disease. *Arch. Int. Med.*, 58, 957, 1936.
- ²² Puppel, I. D., and Curtis, G. M.: Iodine Balance in Exophthalmic Goiter. *Arch. Path.*, 26, 1093, 1938.

MALIGNANT ADENOMA OF THE THYROID, WITH SECONDARY METASTASES TO BONE

WITH A DISCUSSION OF SO-CALLED "BENIGN METASTASIZING GOITER"

RALPH E. OUTERBRIDGE, M.D.

TORONTO, CANADA

FROM THE ORTHOPEDIC SERVICE, TORONTO GENERAL HOSPITAL

DURING the past 20 years on the Public Wards of the Toronto General Hospital there have been performed a total of 2,268 thyroidectomies. Sixty of these thyroidectomies, or 2.6 per cent, were done for carcinoma of the thyroid. Of these 60 cases, 24 were diagnosed as adenocarcinoma or malignant adenoma of the thyroid. Five of these cases of malignant adenoma had metastases to bone.

I should like to limit the scope of this paper to a discussion of the five cases from this group of malignant adenomata, with secondary bony metastases, which were similar to each other in that not only did their symptomatology first direct attention to the secondary tumor, but biopsy of this tumor showed that it was made up histologically, in part, or completely, of apparently quite benign thyroid tissue.

The first case was admitted because of a mass involving the right zygoma, which was made up for the most part of benign thyroid tissue, although portions of the tissue were atypical enough to suggest its malignant nature.

Case 2 presented herself because of a tumor of the parietal bone, which on section proved to be benign thyroid tissue.

Case 3 was sent in because of a destructive tumor of the radius. No signs or symptoms suggested the thyroid gland as the offender until biopsy report was returned as benign thyroid tissue.

Case 4 came in because of a paraplegia of gradual onset involving her lower limbs. Biopsy of a tumor of the 5th thoracic vertebra revealed benign thyroid tissue.

In Case 5, the general pattern differs from the others in that she had a thyroidectomy, because of pressure symptoms, and malignant adenoma removed, only to develop paraplegia from a metastasis in the cervical spine seven weeks later. This was removed, and following roentgenray treatments she has apparently made a complete recovery.

This interesting condition was first described by Cohnheim,¹ in 1876, and called by him "benign metastasizing goiter." That it was possible for a benign tissue to break off cells into the blood stream and form distant metastases of similarly benign tissue, is so contrary to the accepted laws governing histopathology, as to have continued to intrigue the clinician as well as the pathologist since that time. In comparatively recent years, evidence seems to be accumulating to suggest that in spite of their benign appearance, these tumors are actually malignant.

Historically, Cohnheim's original case is of interest because it has been

frequently quoted in the literature to support the theory of the possibility of benign metastases.

A woman, age 35, developed multiple small gelatinous metastases in bronchial nodes, lung, femur and lumbar spine. The thyroid gland was diffusely and symmetrically enlarged, and contained two nodules similar in gross and microscopic appearance to the metastatic seedlings. One of these nodules showed invasion into the lumen of the left inferior thyroid vein. Histologic appearance of the thyroid nodule was that of simple colloid goiter and the metastases revealed a similar cellular structure except that a few small acini contained no colloid and some of the follicles showed the presence of epithelial nests.

Cohnheim concluded that this was a case of simple colloid goiter, with metastases. He skipped lightly over the fact of the invasion of the lumen of the left inferior thyroid vein, saying that it had been noted before in cases with no metastases. He attempted to explain the presence or absence of metastases in these cases of venous invasion by assuming a special constitutional individuality which made metastases possible in some and not in others. Thus, in this original case, the presence of (1) metastases; (2) venous infiltration; and (3) epithelial cell nests make its benign nature, in the light of our present knowledge, highly problematical.

In 1899, Honsell² made a spirited defense of Cohnheim's conclusions. He discussed at some length the possibility of the benign thyroid metastases being displaced thyroid anlagen. Considerable work has been done on this subject and it has become firmly established that although aberrant thyroid tissue is a fairly common anomaly, it is found in places close to the site of its primitive origin. Aberrant masses, derivatives of the thyroglossal duct, may be found in the midline almost anywhere from the foramen caecum in the tongue to the arch of the aorta. Lateral aberrant masses, remnants from the branchial cleft derivatives are found usually about the middle of a line joining the mid-clavicle to the mastoid. In these positions aberrant thyroid gland tissue is commonly found, and is not infrequently associated with carcinomatous changes.

The one exception to this rule of thyroid tissue arrests being found in the neighborhood of the gland origin is in the case of teratomata which are occasionally encountered chiefly in ovaries, testes and the sacral area. This tumor occasionally contains mature thyroid tissue together with the other tissues which go to make up its complex structure.

Bearing these facts in mind, the theory that normal thyroid tissue may develop from developmental cell arrests in scattered foci throughout the body becomes highly unlikely.

In 1926, Simpson³ reported three cases of so-called "benign metastasizing goiter," all of whom died within three years of frank carcinoma of the thyroid gland. In the same paper he reviewed in detail 77 cases reported in the literature of this condition. These were all the cases he could find. He found that the diagnosis in nearly every case was made on the benign microscopic appear-

ance of the secondary tumor and the presence of a clinically benign thyroid gland. Of the 77 cases, a microscopic examination was made in but 29 cases and an autopsy in only 33. Several of the cases hastily reported following pathologic examination of the biopsy from the metastases, were later reported as having died from undoubted carcinoma of the thyroid. He concluded that these cases had been inadequately studied and that existence of the possibility of their being such a thing as benign thyroid tissue seeding the body with innocent metastases was highly unlikely. In recent years it has become generally accepted that in spite of their innocuous appearance, these metastases are actually malignant and are always derived from a primary carcinoma, usually a malignant adenoma, of the thyroid gland.

A malignant adenoma is thought to arise from a fetal adenoma. They vary greatly in size and appearance. They may become large and exert their malignant effect mainly by pressure in the neck or they may remain very small and give rise to metastases which terminate life. They differ chiefly from genuine carcinoma in being encapsulated and being considerably slower in their rate of growth.

The microscopic appearance of the malignant adenoma varies greatly, both in different specimens and in different parts of the same specimen. Most often the appearance is that of cubical or low columnar cells arranged in acini which frequently contain colloid material—while in places the cells may be disposed in solid masses or even present a papillary type of formation. In the same tumor there may be portions resembling normal hypoplastic thyroid tissue in one area, solid carcinomatous masses in another, or papillary adenocarcinoma in yet another.

According to Ewing,⁴ in the metastases from this type of tumor "the microscopic structure is usually of a more adult type than the original tumor and many of the acini appear as fully-developed normal thyroid acini containing colloid. The metastases, however, may differ in their microscopic appearance just as the original primary in the thyroid differs in different parts of the tumor, thus, giving rise to the so-called "benign metastases" and "malignant metastases" depending on the histologic appearance of the metastatic nodule. The character of the tissue found within the metastatic nodule corresponds always in morphology to some portion of the original tumor, though it is not always possible to demonstrate the histologic criteria of malignancy in it."

Graham⁵ concluded from his studies that the morphologic characteristics of the cells and tissue structure was an unreliable method of determining the presence of malignancy. He felt that in his series that only 30-40 per cent of malignant epithelial tumors of the thyroid could be diagnosed by the histologic appearance alone. The most constant single indication of epithelial malignancy was the invasion of blood vessels. It is probable that metastases from these tumors originate at such a site and travel to their proliferative focus *via* the blood stream.

Reinhoff⁷ makes the statement that "there is an inherent tendency on the part of thyroid cells that have passed into the blood stream or lymph circula-

MALIGNANT THYROID METASTASES

tion, after becoming lodged in an organ or tissue, to develop into normal thyroid tissue, so that, after metastasizing, an original carcinomatous area may appear benign. Metastases from normal thyroid do not occur."

CASE REPORTS

Case 1.—(A25011): A. R., male, age 42, of Scottish descent, carpenter, was first admitted in February, 1937, with a history that 18 months earlier he first noticed a small lump just in front of his right ear. It was about the size of an olive, hard, painless, and, at the onset, associated with some stiffness of the right side of the neck. A month later he noticed increasing fatigue which symptom together with a loss of 25 pounds persisted until his admission. The lump gradually increased in size.

Upon admission to hospital, he had a large pulsatile swelling the size of half an egg over the right zygoma and a similar mass involving the 5th rib in the anterior

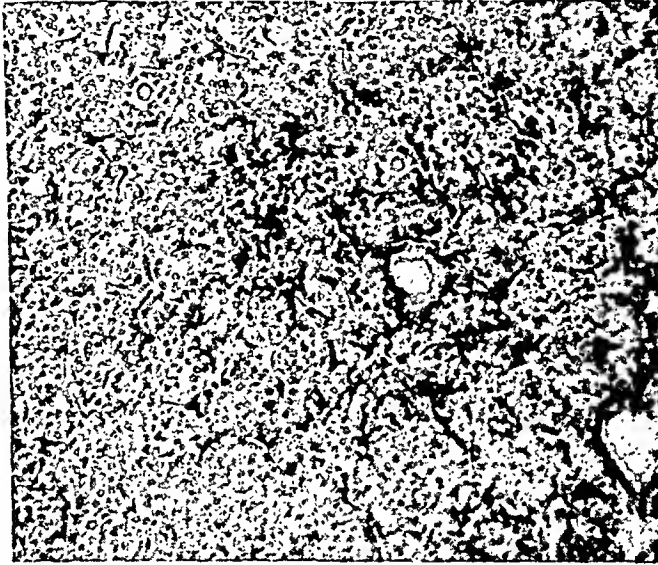


FIG. 1.—Case 1: S-37/472. Secondary metastasis showing tendency of cells to form cords.

axillary line and a third pulsating mass over 2L vertebra. A small hard nodule the size of a bean was felt in the right lobe of the thyroid. There was nothing of significance on blood examination. His Wassermann was negative. B. M. R. was +37. There was no definite sign or symptom suggestive of hyperthyroidism.

Biopsy (S—37/472) taken from the tumor of the right zygoma revealed an extremely cellular mass, sections of which reproduced fairly typical thyroid gland acini. These acini were well filled with colloid material. Other sections showed cuboidal cells growing in small compact pseudo-acinar arrangements and in cylindrical cords (Fig. 1). In several areas invasion of blood vessels was noted and its malignancy was further demonstrated by the atypical characteristics of the individual cells, their lack of polarity, abundant mitotic figures as well as the inability of the tissue to accurately reproduce thyroid tissue throughout.

A partial thyroidectomy was then performed and the right lobe containing two adenomata removed but the left which felt quite normal was not touched. At the time of operation it was noted that the gland was easily freed, with no evidence of invasion beyond the capsule of the adenoma.

Section of the right thyroid lobe (S—37/893) revealed a normal gland except for these two adenomata made up of the same malignant composition as their metastases. A re-check B. M. R. shortly after his thyroidectomy was +45.

This man was then referred to the Radiologic Department for treatment of his secondaries with deep roentgen therapy which began in March, 1937.

Roentgenologic examination, December 17, 1937, revealed further secondaries in L1 and L4, left pubic and right wing of ilium.

February 3, 1939, it was noted that the lesion on the right temporal area had diminished somewhat in size and had become softer as a result of high voltage therapy. However, it had not disappeared and, as its reaction to treatments was being used as a therapeutic test of radio sensitivity, the conclusion was drawn that these metastases were fairly resistant to the roentgenray.

He was again admitted in June, 1939, because of a large metastasis involving his left femur. He was fitted with a walking caliper on this admission. Examination on this second occasion revealed the fact that although the roentgenray treatments had helped to partially relieve his pain it was unable to check the growth of the secondary tumors.

He developed a spastic paraplegia and cord bladder in August, 1939, and died in June, 1940, just five years after the onset of his trouble.

Postmortem Examination.—(No. 1241): The site of the primary tumor was represented by a small amount of partially fibrosed thyroid tissue. The metastases, which were composed for the most part of fairly typical thyroid acini, were confined entirely to the osseous system. They were discreet and growth had occurred almost entirely in an expansile manner with very little tendency toward invasion of the surrounding tissues. There was a large circumscribed tumor of the right zygoma and temporal bone which had destroyed the bony plate of the skull and, by expansion beneath the dura, had compressed the underlying temporal lobe. Similar circumscribed tumors were attached to both the 5th rib and the right ischium and there were extensive deposits in the vertebrae, with two pathologic fractures. Compression of the cord by tumor in the midthoracic region accounted for the patient's paraplegia. The left femur at the junction of the middle and upper thirds showed partial destruction by tumor.

Case 2.—(A28225): Mrs. A. S., female, age 73. This patient was first treated in this hospital in April, 1937, at which time she had a spinal cord tumor removed from the level of the 1st thoracic vertebra. This tumor on pathologic examination proved to be a meningioma.

In October, 1945, she was again admitted—this time because of a tumor of the skull. She stated that eight months previously, she had fallen and bumped her head and two weeks later noticed a swelling of the left parietal region. This has been increasing slightly in size but gave her no trouble. On admission, it was noted that she had a firm, painless nodule the size of a walnut in the left parietal region which lay deep to the skin and was attached to bone. A roentgenogram showed a punched-out decalcified area about 1.5 inches in diameter. Her thyroid gland contained two small, firm, painless nodules.

The tumor of the skull was removed (S—5711/45) together with a surrounding block of bone, of both the inner and outer tables which had been eroded through. There was no evidence of invasion of scalp or dura. Because of her age it was felt unwise to do more than remove the secondary tumor locally.

Pathologic examination revealed a reddish hemorrhagic appearance of the tumor on cut-section. It contained multiple cystic spaces of varying sizes some of which contained colloid.

The microscopic examination revealed typical benign thyroid tissue.

The thyroid alveoli were well-formed. They were lined by a single layer of cuboidal-to-columnar epithelial cells. Their lumen contained colloid. There was no evidence of malignancy of this thyroid metastasis. There was no evidence of infiltration of tumor cells into the surrounding bone or the scalp tissues overlying the outer table.

Case 3.—(B82194): Mrs. V. S., female, Polish, age 41, housewife. Admitted February 28, 1946, with a history of occasional pain down the right forearm and wrist for three years, noticed chiefly on movements of supination, such as wringing out the

clothes. Pain, however, has never been a marked feature of her story. One and one-half years ago she struck her right forearm, following which she noticed the gradual development of a lump.

On admission, there was a firm, pulsating, slightly tender mass, the size of an orange, involving the upper and outer aspect of the right forearm.

Roentgenograms showed the tumor to involve the upper one-quarter of the right radius, with the exception of the head and 0.5 inch of neck. There was complete destruction of the shaft of the bone, the destructive process beginning abruptly from apparently normal bone at each end. A fine network of radiopaque threads ran through the mass, the picture suggesting a mass of soap bubbles (Fig. 2). The roentgenograms suggested benign giant cell tumor or possibly an osteolytic sarcoma. Roentgenograms of the remaining osseous system failed to disclose other tumor masses.



FIG. 2.—Case 3: (262158) Roentgenographic appearance of secondary tumor of the radius.

It was not until a biopsy (S—46/1266) was done that the true nature of the condition became apparent. The section consisted of connected cords of acidophilic cells grouped in alveolar formation and containing colloid (Fig. 3)—a typical picture of benign metastasizing tissue.

There was nothing to suggest, in the history or the examination, the possibility of hyperthyroidism. B. M. R. was +8. Two very small nodules were palpable in the right lobe of the thyroid.

A subtotal thyroidectomy was performed March 22, 1946, at which time two adenomatous masses were found, one benign and the other malignant (S—46/1662). The malignant adenoma was made up mostly of fairly typical thyroid cells lying in cords or in irregular masses within a thick capsule (Fig. 4). In the adjacent tissue were found veins completely filled with parenchymal cells similar to those of the adenoma (Fig. 5).

March 31, 1946, the tumor of the radius was resected together with the normal-appearing head at one end and part of the shaft at the other. The tumor was soft, encapsulated and contained filmy shells of bone which broke under the examining fingers like fresh corn flakes.

Following operation her B. M. R. was +4.

Case 4.—(B67357): Mrs. B. B., female, age 67, housewife. Following a fall two years ago this patient noticed the gradual onset of weakness and numbness in both legs. When first admitted, in March, 1945, she had complete loss of motor power of both legs, and loss of pain, touch and vibration sense below the xiphisternum level. There was urinary retention. Blood Wassermann was negative.

Roentgenograms revealed a tumor, thought to be an hemangioma, involving the 5th thoracic vertebra and the proximal portion of the posterior end of the 5th left rib.

Laminectomy was performed in April, 1945, and a very vascular tumor removed. Microscopic examination (S—45/1943) revealed thyroid tissue which, on the whole, was benign in appearance but in portions showed the presence of mitotic figures and a heaping-up of epithelial elements. There was a definite infiltration of the ligamentum subflavum.

The right lobe of the thyroid was enlarged. This enlargement had been present since adolescence though was possibly somewhat larger at present.

FIG. 3



FIG. 4



FIG. 5

FIG. 3.—Case 3: (S—46/1266) Secondary metastatic tumor. In one corner is a fragment of bone of the radius. The remainder of the section shows normal-appearing thyroid tissue making up the substance of the secondary tumor. (x 160)

FIG. 4.—Case 3: (S—46/1662) A vein in the wall of the primary adenoma, filled with tumor cells. In one corner can be seen normal-appearing thyroid acini filled with colloid. (x 65)

FIG. 5.—Case 3: (S—46/1662) High power showing a section of the vein wall with tumor cells filling the lumen and normal-appearing thyroid tissue on the outside. (x 300)

She received during the last year a total of four courses of deep roentgenray treatments to the thyroid gland and 5th thoracic spine area.

Her last admission to hospital was in April, 1946, for her 4th deep roentgenray series. At that time her thyroid gland was still enlarged—not showing much diminution in size since before her treatments. Her neurologic examination, however, revealed a very definite improvement.

Sensory involvement had completely returned from xiphisternum down to her knees, though remained somewhat impaired below that level.

Bladder function had returned to normal.

Motor power was not present in all muscle groups though still not sufficient to allow her to bear weight.

Case 5.—Mrs. W. C., female, age 30. This patient developed an adolescent goiter at the age of 12, which did not increase in size until November, 1941. A thyroidectomy was performed three months later because of pressure symptoms and the pathologic examination (2—42/469) showed thyroid tissue which, on the whole, was suggestive of a simple thyroid adenoma with some cystic degeneration, but the presence of a few small areas of atypical cell formation together with evidence of blood vessel infiltration with parenchymal cells, established the diagnosis beyond doubt of its malignant nature.

Two months later she noticed the gradually increasing development of a weakness and numbness of both lower limbs. Examination at that time showed an incomplete spastic paraplegia, paresthesia and some sensory loss involving the lower portion of her trunk and lower limbs. She could not get upstairs except by crawling on her hands and knees.

Radiologic examination revealed evidence of bone destruction of 7C and 1T. vertebrae and double spinal puncture established the presence of a complete block at that area.

A cervical laminectomy was performed May 26, 1942, and a bluish-purple, granular mass, involving and softening the laminae of C7 and T1 and lying within the extradural space, was found. It was technically possible to only partially remove this tumor which, on section (M. P. 153-42), showed a typically benign type of thyroid tissue.

This patient was then given a total of five series of teluradium to the region of the cervicodorsal spine. She has shown gradual and steady improvement. She now works in a bottle factory, standing on her feet eight hours a day. Her stance and gait are normal. Sensory return has been complete. Other than an occasional aching pain in her left hip and calf noticed after a strenuous day, she has no complaints whatsoever.

DISCUSSION AND CONCLUSIONS

These cases well illustrate the main features of this condition and may be briefly summarized:

(1) The patient usually first comes to hospital because of symptoms produced by the bony tumor. In this way these cases simulate those of carcinoma of the prostate or of hypernephroma which frequently give signs of bony metastases before the primary new growth has been found.

(2) Despite the benign appearance of the histopathology of these metastases, if a careful search is made, a malignant primary focus can always be found in the thyroid gland.

(3) This primary process is nearly always a well-encapsulated adenoma which for some unknown reason has become malignant, invading local blood vessels and spreading to some distant portion of the skeletal system *via* the blood stream.

(4) In our series only 33 per cent of malignant adenomata had formed

metastases by the time the primary growth was removed from the thyroid gland.

(5) Secondaries from this type of tumor have a predisposition for the osseous system in which to settle. The bones most likely to become involved are shown more accurately in Simpson's review of 77 cases. He reports:

Skull.....	30	Femur.....	9
Vertebrae.....	25	Ribs.....	9
Pelvis.....	11	Humerus.....	7
Clavicle.....	9	Scapula.....	3
Sternum.....	9	Mandible.....	2

(6) These metastatic tumors have a tendency to invade bone by growing in an expansile manner, eroding the bony cortex and giving a radiographic picture somewhat similar to osteolytic sarcoma or giant cell tumor.

(7) The bony metastases are frequently pulsatile and occasionally enlarge during menstruation and pregnancy, although this latter observation was noted in our series.

(8) No conclusion can be drawn from these cases in regard to the interesting problem of hyperthyroidism associated occasionally with these tumors. Case 1 had a B. M. R. of +37 which rose to +45 one month after thyroidectomy.

Reinhoff⁹ states that "it is very unlikely that hyperthyroidism ever occurs in the absence of histologic evidence of hypertrophy and hyperplasia of the thyroid epithelium whether associated with a benign or malignant tumor. As a rule, the symptoms of hyperthyroidism accompanying malignant tumors of the thyroid are very mild.

Treatment.—Complete excision of the primary malignant adenoma and metastases would seem to be the most rapid and effective means of dealing with this problem. This we hope to have accomplished in Case 3, in whom the primary in the thyroid and the only demonstrable secondary, that involving the radius, were removed. Removal of the secondaries alone is not enough, as the primary, if left, will continue to give off metastatic emboli.

The effectiveness of this means of treatment depends on removal of both primary and secondaries early, before multiple secondaries make this procedure technically impossible. The slow growth of this tumor is in the surgeon's favor. Our cases suggest that one has at least a year after the formation of the first metastatic tumor, before others begin to develop. The importance of recognizing the malignant nature of this condition cannot be over-emphasized.

Deep roentgenray therapy seems to have found a definite place in the treatment of this condition. There have, however, been an insufficient number of cases treated over too short a period of time to come to any definite conclusion as to the effectiveness of this treatment.

Case 1 continued over a period of three years, during which he received radiation, to slowly, but inexorably, deteriorate until his death, when autopsy revealed large and multiple metastases.

Case 4 has now been treated for one year, during which her symptoms of

THORACIC SURGERY IN A HOSPITAL CENTER

COL. LAURENCE MISCALL, M.C., A.U.S.

AND

MAJOR ALBERT W. HARRISON, M.C., A.U.S.

PART II

ABDOMINOTHORACIC INJURIES

Abdominothoracic injuries admitted to the Center have presented characteristics which set them apart as a group. Severe initial injury has been followed by a multiplicity of complex problems of rather constant origin. The right side has differed from the left although the course for each has been quite typical. They have required close correlation of thoracic and abdominal procedure.

Of 28 abdominothoracic injuries secondarily treated at the Center, 18 were on the right side and 10 on the left. Thoracic exploration had been done in 13; abdominal exploration in seven, and combined through the same or separate incisions in eight. After intrathoracic procedure, only six chests had been drained. The diaphragm had been almost routinely closed with interrupted silk. Subphrenic procedure had involved the spleen, intestines, kidney, liver and other viscera. Abdominal or flank drainage of the subphrenic area was limited to four on the right side.

On the right side, 18 cases were diversely distributed. Seven patients had empyema, with transdiaphragmatic bile fistulae. All were massive and had been repeatedly aspirated for fluid containing bile. Clinically, they had been only mildly toxic. None had progressed to constrictive pleuritis, necessitating decortication, if a bile fistula freely communicated with the space. All have responded well to closed and subsequent open dependent thoracic drainage. Two residual transthoracic biliary fistulae healed with diversion of the biliary stream to the exterior by radial incision of the diaphragm.

Suppuration above and below the diaphragm coexisted in four patients. Interposition of the diaphragm with separate thoracic and subphrenic drainage were extensive procedures, but uniformly successful. In two, spontaneous closure of fistulae had cut-off free flow of bile into the thorax. Suppurative constrictive pleuritis of clostridial origin followed, and had the only two decortications on the right side. One patient had severe hemorrhage from a suppurating liver defect which required pedicle muscle graft and thoracoplasty.

Subphrenic suppuration without thoracic involvement occurred in seven cases. It uniformly followed premature healing of drainage sites with reaccumulation of infected bile. All recovered with drainage across the diaphragm and obliterated pleural space. One recurrence was reoperated. Localized abscesses around intrahepatic foreign bodies have been rare. Secondary empyema followed such foreign body extraction and transpleural drainage in one case.

The situation on the left side was different. Suppuration was limited to

the thorax in six cases, to the subphrenic area in one, and combined in only three. Seven cases required decortication for suppurative constrictive pleuritis but only two acute empyemata were drained. Three diaphragmatic repairs and one splenectomy were done. Two subphrenic collections were drained and two were closed after instillation of penicillin. There were no deaths in any abdominothoracic cases.

Some points deserve emphasis. Infection as a uniform complication of abdominothoracic injuries has been associated rather constantly with insecure closure of the diaphragm and lack of thoracic and subphrenic drainage. Suppuration in these severe injuries has predisposed to severe illness.

On the right side, bile empyema, with a high incidence of *Clostridial* infection, has been common. They have done well on drainage and required few decortications. On the left, suppurative constrictive pleuritis necessitating decortication has predominated. No *Clostridia* have been observed. Diaphragmatic herniae and intrahepatic foreign bodies have not been as important as expected. The surgical problems in these cases have been complicated and required a diversity of methods. Adequate correlation has been often possible only with extensive procedures. Chronic biliary fistulae and suppuration may recur in many of these patients.

FOREIGN BODIES

Although foreign body removal has been the most frequent procedure in this study, its numerical prominence does not signify similar surgical importance. Incidental tissue damage and sequelae have generated more problems than the retention. They can be presented best as a separate entity but not always considered a separate problem.

Small bodies (less than 1.5 cm. in all diameters) have been associated with little tissue damage and few sequelae. As parenchymal bodies they have been well-tolerated and usually asymptomatic except in the heart. None have abscessed or bled. Some in the pleura have caused persistent hemothorax but empyema has followed only rarely.

Large bodies have often damaged tissue severely and implanted infected material. Retention of them must share with all other factors a fair responsibility for the high incidence of late sequelae. Fifteen (71 per cent) of 21 foreign bodies in or communicating with the pleural space were associated with late sequelae: clotting occurred in ten cases, and eight of these suppurated. Five had acute empyema. In the lung extensive surrounding reaction has generally cleared. Some have been surprisingly asymptomatic. Others have had irregular sputum, hemoptysis and unexplained pain. Eight abscesses formed around two fragments and in six tracts. Two of these also had interlobar empyema. The course of rib fragments has similarly depended on size and persistent defects.

One hundred and thirty-eight foreign bodies have been removed from the thorax: 98 as a primary elective procedure and 40 as an incident during surgery for other cause.

LUNGS AND PLEURA

Sixty-eight foreign bodies in the lungs were evenly divided between the two sides. Although most had recovered from a mild antecedent hemothorax some were removed and minor clotting cleaned-up at the same time. Accurate location has always preceded operation. It has been often possible to extract those near the thoracic wall by incision through an area of adhesions. In the more centrally placed, the lung usually has been free or only lightly adherent.

A



B



C

FIG. 7.—H-8569: Injured: August 6, 1944. Right abdominothoracic wound
A. August 15, 1944. Right empyema, subphrenic abscess, thoracic wall fistula
(*Clostridia welchii*).

B. September 3, 1944. Result 16 days after open thoracic drainage and radial
incision of diaphragm.

C. October 19, 1944. Result 62 days after operation.

To insure safety, the thorax has been opened widely except in a few near the fissures. The lung has been freely incised to allow visual extraction. The residual cavities have been treated by various methods. All have been thoroughly washed with saline and 10,000 units of penicillin instilled. An occasional large peripheral cavity entered through adhesions was drained by a small tube which was penicillin-irrigated during gradual withdrawal over 48

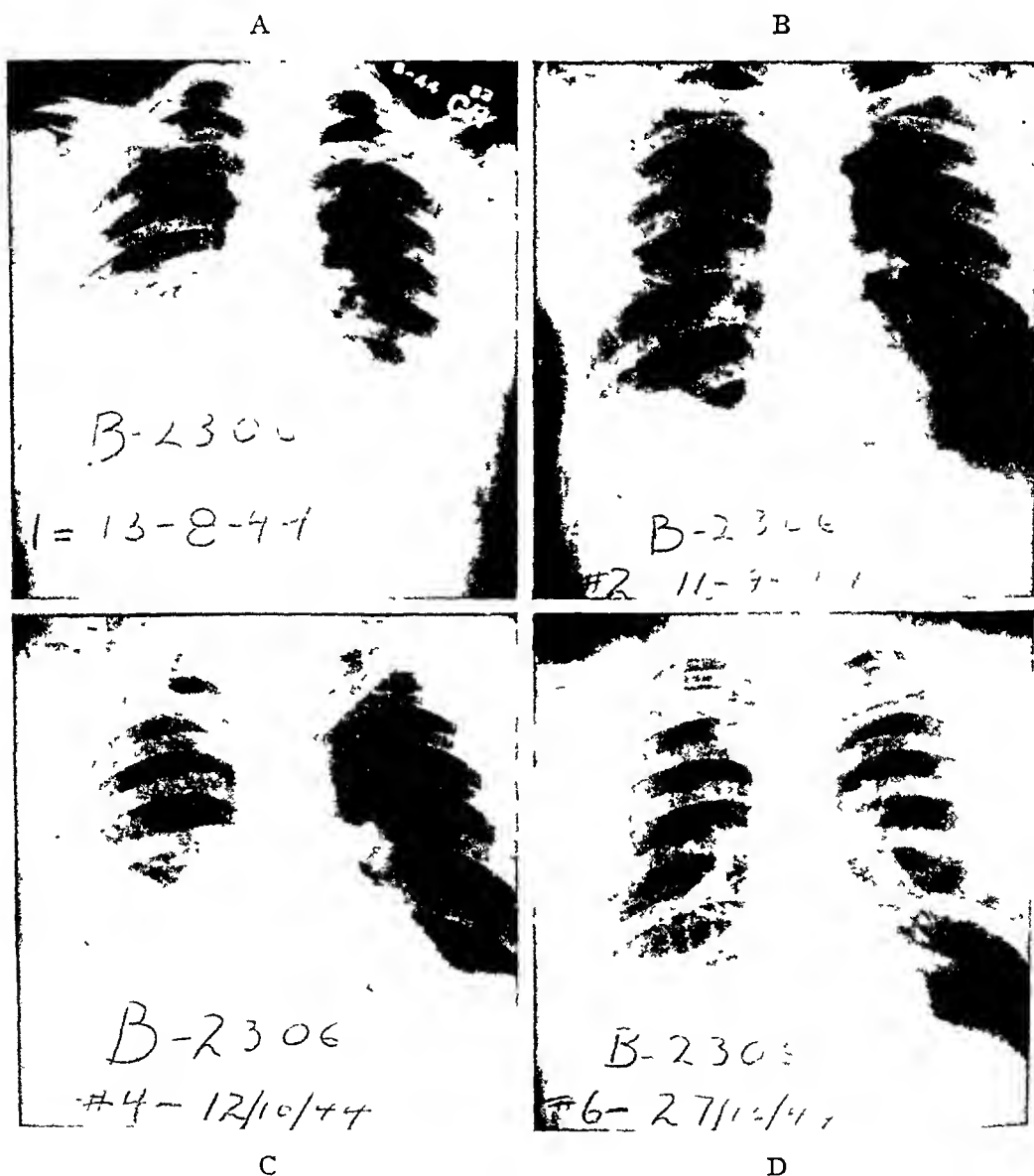
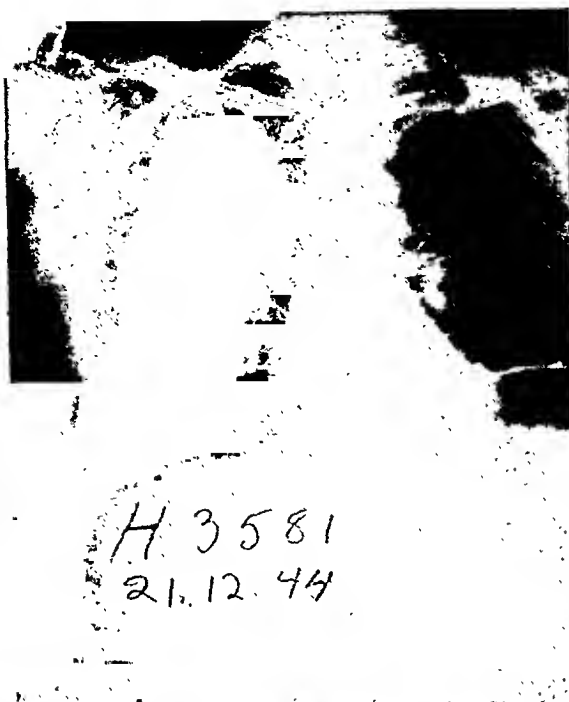
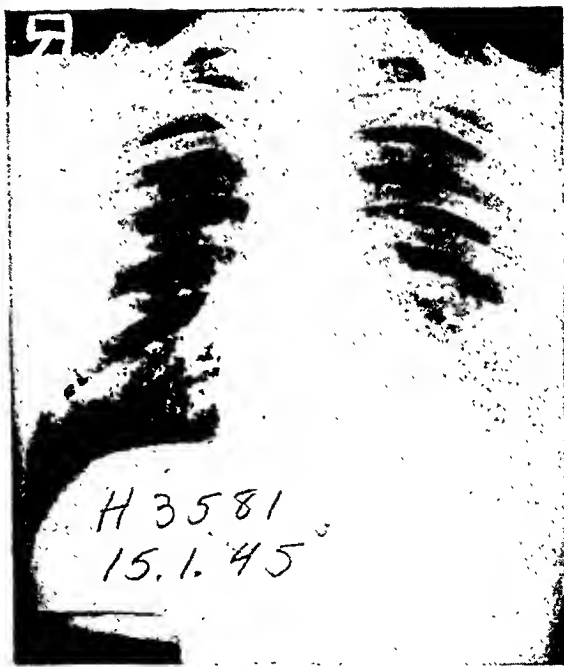


FIG. 8.—B-2306: Injured: July 14, 1944. Abdominothoracic wound, right.
A. August 13, 1944. Right empyema and subphrenic abscess with biliary thoracic fistula. (*Clostridia welchii*).
B. September 9, 1944. Result 27 days after drainage of right chest and subphrenic space.
C. October 12, 1944. Recurrent empyema and right subphrenic abscess.
D. October 20, 1944. Result 8 days after redrainage of right chest and radial incision of right diaphragm for subphrenic abscess.

A



B



C

FIG. 9.—H-3581: Injured: November 24, 1944. Left abdominothoracic wound. Repair of lacerated diaphragm at original operation.

A. December 21, 1944.

B. December 28, 1944. Diaphragmatic hernia left, with incarcerated stomach.

C. January 15, 1945. Result 12 days after splenectomy for lacerated spleen, with secondary hemorrhage and suppuration and repair of diaphragmatic defect.

hours. All others, with or without free opening of pleura, have been closed without drainage. Control of fistulae, hemorrhage and approximation of pleural edges has not been difficult with a few fine (No. 120) interrupted cotton sutures. In a few the wall was excised before closure if changes prevented ready collapse. Pleural spaces that were freely opened were drained generally for 48 hours by a single basal catheter after the insertion of penicillin. Bronchoscopy has been routine.

In spite of positive cultures in 62 per cent of these cases, no secondary empyema nor abscesses have occurred. All have had primary wound union, and were ready for rehabilitation in 21 postoperative days.

Only six of 21 metallic bodies removed from the pleural space have not been associated with clotting or suppuration. The elective extraction of these has been simple and without complications.

Forty foreign bodies removed as a part of other procedures have been either in the lung or pleura. Most important have been those lying in the apex of a fistula which prevented its closure and predisposed to suppurative constrictive pleuritis. Removal of 38 has been without complication. In two clean decortications, positive cultures around foreign bodies may have contributed to secondary empyema.

MEDIASTINUM

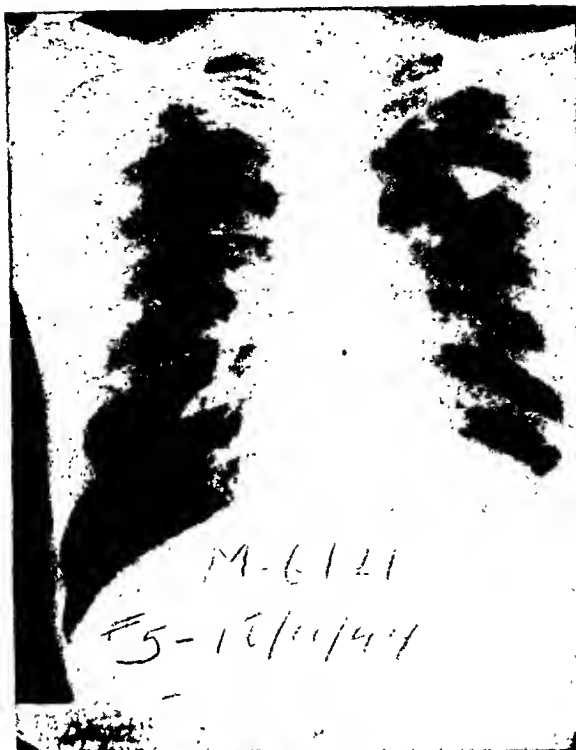
Ten foreign bodies have been removed from the mediastinum. They were asymptomatic and without complication. Four were removed extrapleurally and six transpleurally, with uneventful recovery. One patient with penetration of the lung and mediastinum developed a superior mediastinal and retropharyngeal suppuration, with a tracheo-esophageal fistula. He had respiratory obstruction in spite of a tracheotomy. Emergency enlargement of the tracheotomy opening, through which an endotracheal anesthesia had been administered, permitted the one instance of heroic surgery. Through bilateral cervical incisions joined in the midline at the suprasternal notch, the abscess was drained and the trachea separated from the esophagus after partial thyroidectomy. He completely recovered after tube-feeding for only ten days.

HEART AND GREAT VESSELS

Twenty foreign bodies directly involving the heart or great vessels represent 10 per cent of the total cases operated upon, but 20 per cent of the bodies electively removed. They were in the following locations:

a. Right auricular wall.....	3
b. Right ventricular wall.....	4
c. Right ventricular chamber.....	1
d. Left ventricular wall.....	2
e. Interventricular septum.....	1
f. Within the pericardium.....	3
g. Superior or inferior vena cava or innominate vein.....	3
h. Pulmonary arteries.....	3

A



B



C

FIG. 10.—M-6121: Injured: September 7, 1944. Penetrating wound left chest.
A. & B. October 18, 1944. Asymptomatic foreign body in periphery of left upper lobe,
without reaction.
C. October 29, 1944. Result 10 days after operation.

All of these patients failed in the forward areas to react favorably to usually effective treatment for rather common hemothorax or hemopneumothorax. Fluid tended to persist. In about half, a correct diagnosis was made promptly by either clinical or roentgenologic criteria of hemopericardium. These improved immediately with aspiration. In the remainder, the picture was so masked that they went unrecognized until admitted to the U. K. Hospitals.

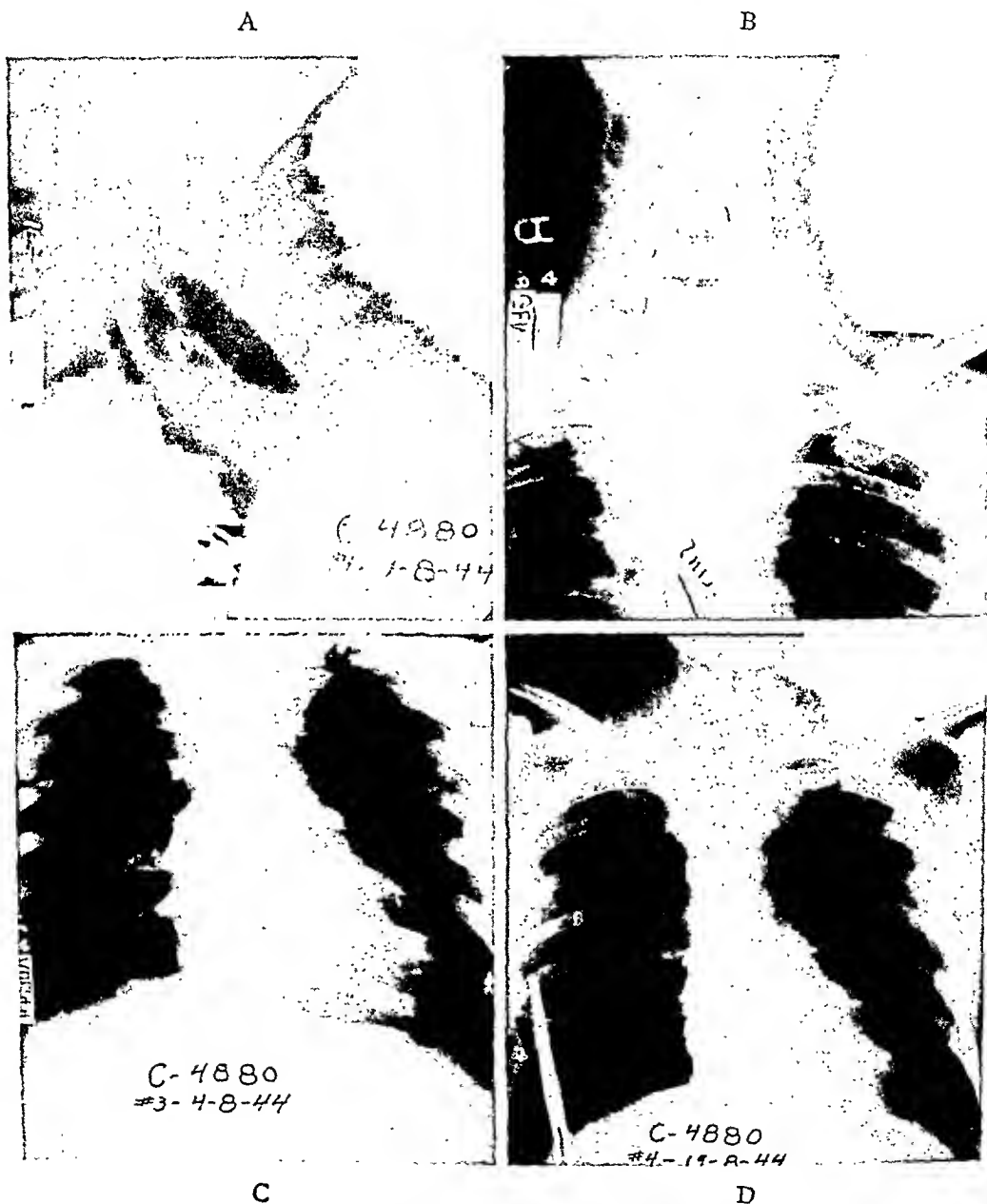


FIG. 11.—C-4880: Injured: July 30, 1944. Penetrating wound of neck left chest with tracheo-esophageal fistula.

A. August 4, 1944. Postpharyngeal abscess containing air;

B. & C. foreign body in neck; superior mediastinal abscess and subcutaneous emphysema.

D. August 19, 1944. Result 15 days after operation. The procedure is described in the text.

Findings in subsequent diagnosis have varied. Some have been practically asymptomatic, with inconstant, minor precordial pain. Syncopal attacks resembling coronary thrombosis or acute pericarditis have recurred and drawn attention to the heart, without adequate explanation. An enlarged cardiac outline or foreign body have been found on physical examination or in roentgenograms. Superposition due to oscillation with the heart has been typical. However, repeated roentgenograms have not shown many because of motion, small size or pleural exudates. Films with high power and short exposure, or fluoroscopy, have been frequently necessary to visualize and locate them accurately. Electrocardiographs, generally, have been abnormal and variously interpreted, with a predominance of pericarditis.

Cardiac bodies have been extracted through a left transpleural parasternal incision curved out over the 4th or 5th interspace. Mobilization of musculo-cutaneous flaps, with division or resection of costal cartilages, has been very satisfactory for exposure and closure. Sternal splitting, extrapleural and other incisions have been utilized less and only as necessary. Trap-door opening of pericardium has been hinged just anterior to the phrenic nerve. Several points of technic have proven of particular value. Adequate exposure of the apex has enhanced ease and safety of operation. The liberal intrapericardial application of procaine (5 per cent) before manipulation has prevented arrhythmia. Hammock sutures routinely placed underneath the foreign body in the cardiac wall, and often traversing a chamber, have steadied it during removal. They have prevented displacement into the heart, which often has been opened. Closure has been accomplished with little loss of blood by crossed-tension on them and a few interrupted sutures of cotton. Then the hammock sutures have been removed. This has been more satisfactory than apical and parallel mattress sutures and without discernible ill consequence.

An adhesive obliterative pericarditis had to be freed in every case in which the foreign body traversed the pericardial space. It has been drained into the pleural space by neglecting to close the inferior portion of the pericardial incision. Four partial pericardiectomies have been done for constrictive lesions. Opening of the left pleural space has been followed by closed drainage after pericardial and pleural instillation of 100,000 units of penicillin. Although eight (40 per cent) of the fragments have yielded positive cultures, secondary suppuration has not occurred in any case.

Foreign bodies in, or communicating with, the lumen of great vessels have been removed after control of the circulation by temporary ligatures to prevent hemorrhage and air embolism. The defect has been easily closed by interrupted cotton sutures except for one pulmonary artery branch ligation. Heparin has been used in only one case. One minor infarction followed suture of the pulmonary artery but improved rapidly. This has been the only adverse incident in six cases.

Roentgenograms showing early cardiac enlargement have returned to normal in 21 to 28 days. Electrocardiographs have not shown changes which

can be attributed to surgery. They have not regressed, but generally improved. No deaths and no significant postoperative complications accrued as the result of this work. The risk of one foreign body lying in the posterior auricular right wall did not warrant removal.

A



B



C

FIG. 12.—S-6269: Injured: December 12, 1944. Gunshot wound of left chest. Left hemothorax treated by aspiration.

A. January 3, 1945.

B. January 5, 1945. Bullet in pericardium.

C. February 13, 1945. Result 28 days after operative removal and partial pericardectomy. (Culture of foreign body—gram-positive cocci).

All E. K. G.'s interpreted as indicative of pericarditis. Returned to normal 35 days after operation.

Three unusual cases deserve special attention.

A shell fragment broke loose as an embolus from a right femoral arterio-venous fistula and, traversing the heart, lodged at the base of the right lower lobe. The artery was opened distal to the foreign body, which was extracted with a small hemostat and the branch ligated. The infarcted section, which had broken down, was shelled-out easily and the middle lobe was laid over this area. Immediate recovery was uneventful. Subsequent rapid cardiac dilatation secondary to emphysema, infarction and the fistula required closure of the

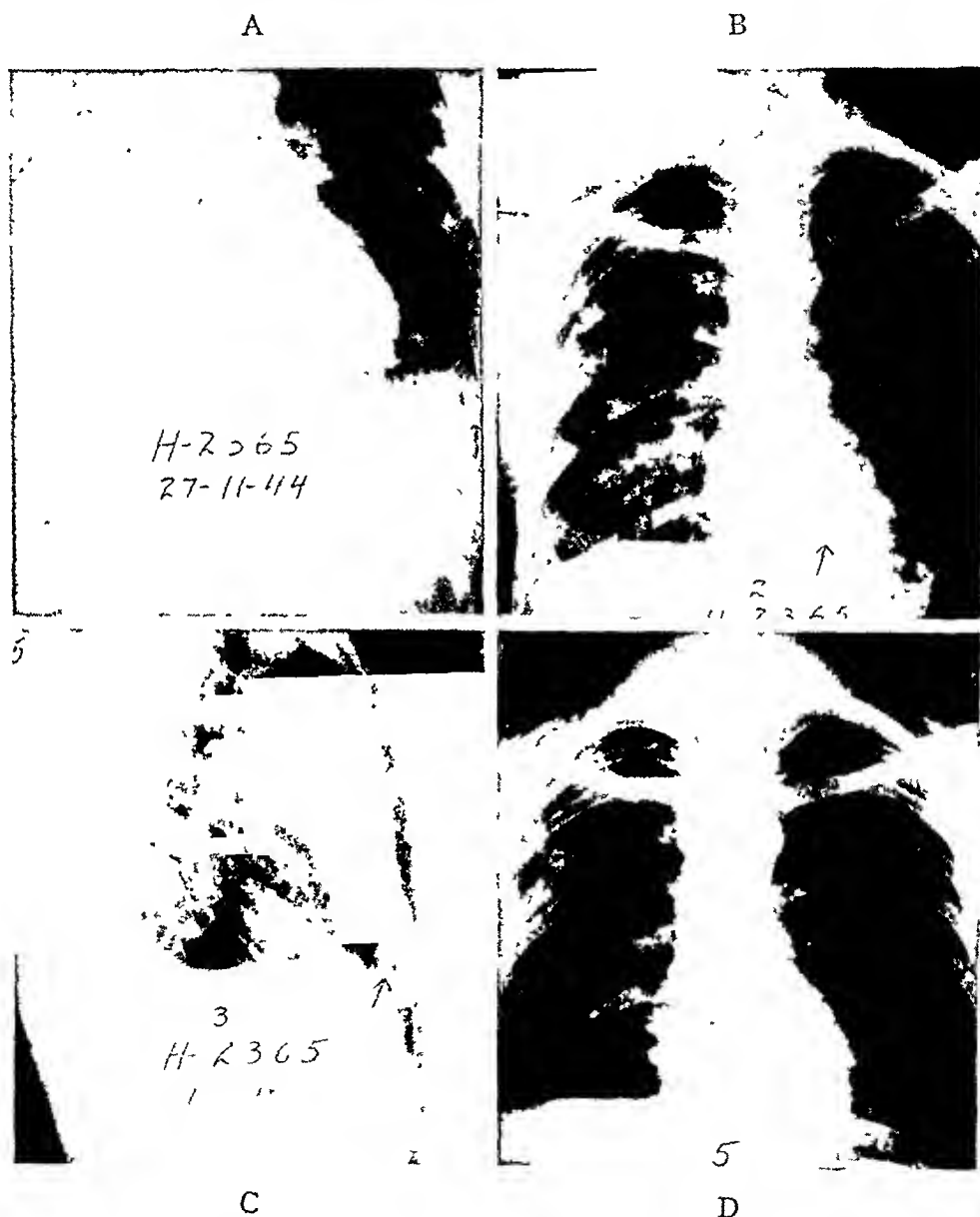


FIG. 13.—H-2365: Injured: November 22, 1944. Penetrating wound right chest and pericardium. Débridement and closure of wound with closed drainage at original operation.

A. November 27, 1944. Right hemothorax and hemopericardium.

B. & C. January 1, 1945. Foreign body in wall of right ventricle which projected into the ventricle-adhesive pericarditis.

D. February 13, 1945. Result 28 days after removal. An E. K. G. interpreted as indicative of pericarditis. After removal without pericardiectomy they returned to normal in 35 days.

fistula. After this was dissected and the continuity of the artery and vein established, the heart rapidly returned to normal size, without symptoms. Heparin, whiskey and sympathetic block were used and may have contributed to a rapid recovery.

Another shell fragment imbedded between the left lower lobe bronchus and the pulmonary artery projected into the latter, with a resultant hemothorax, which cleared. With mobilization of the artery the body was removed and

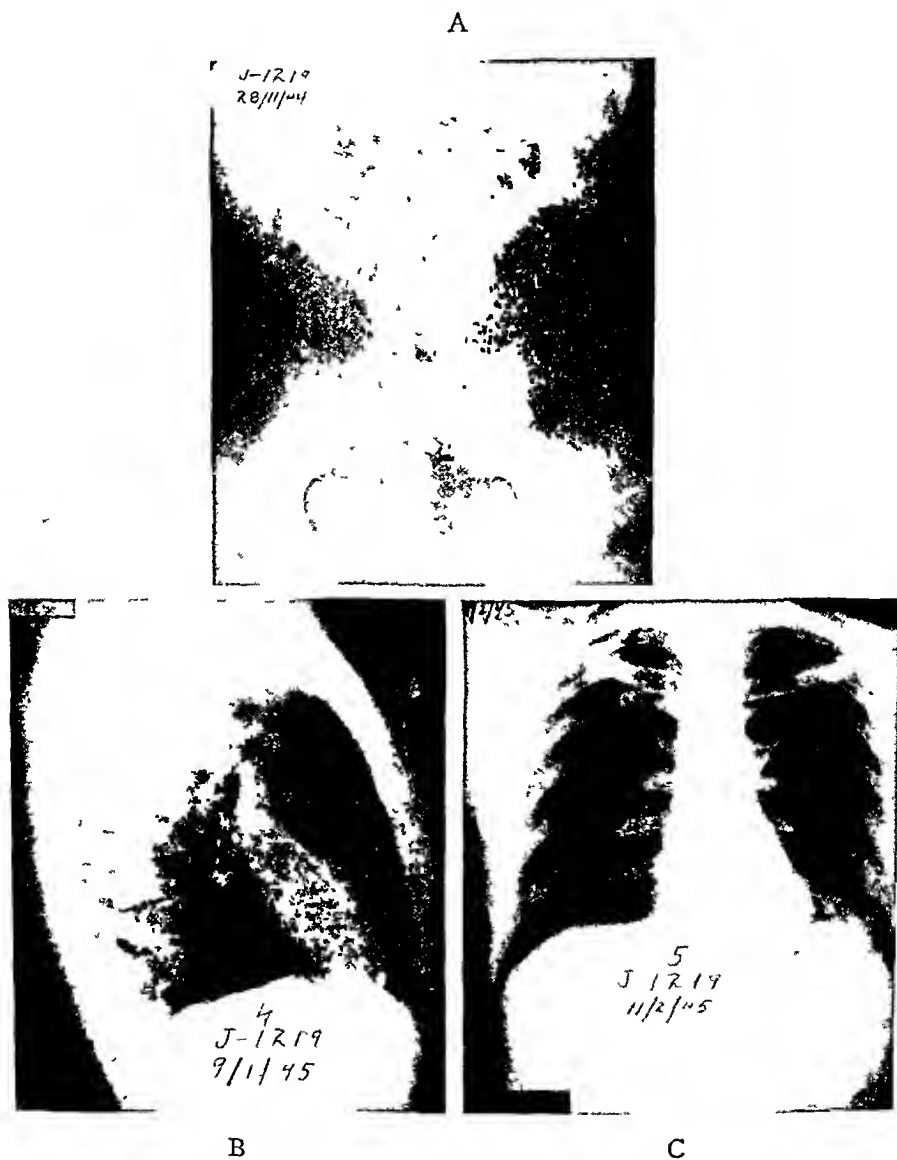
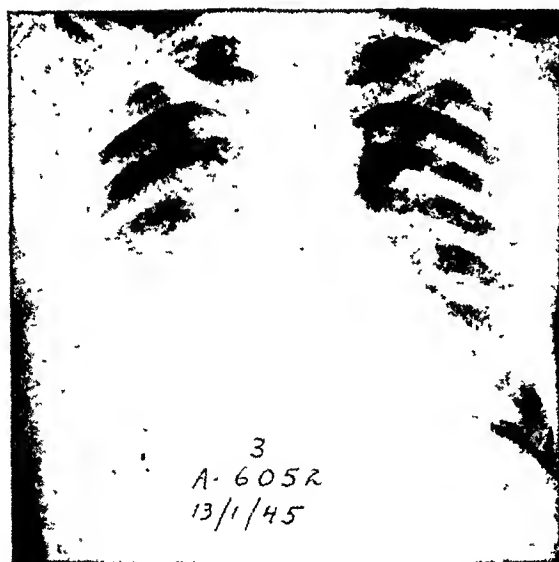
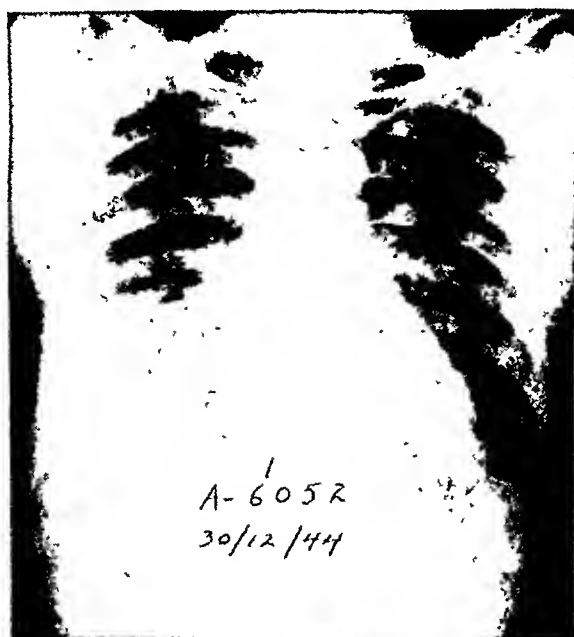


FIG. 14.—J-1219: Injured: November 28, 1944. Shell fragment wound of abdomen. Exploratory celiotomy fragment not found.
 A. November 28, 1944. Shell fragment not found at celiotomy on day of injury. Subsequent roentgenograms showed it had disappeared.
 B. January 9, 1945. Shell fragment embolic to right ventricle.
 C. February 12, 1945. Result 21 days after removal from right ventricle.

the vessel successfully sutured. Neither heparin nor whiskey were used. Recovery was uneventful in spite of minor infarction of the left lower lobe, which cleared completely.

After abdominal wounding, a shell fragment was visualized in the pelvis but subsequent examination disclosed it to be in the heart. It was removed

A



B



C

FIG. 15.—A-6052: Injured: December 12, 1944. Shell fragment wound of right femoral artery and vein.

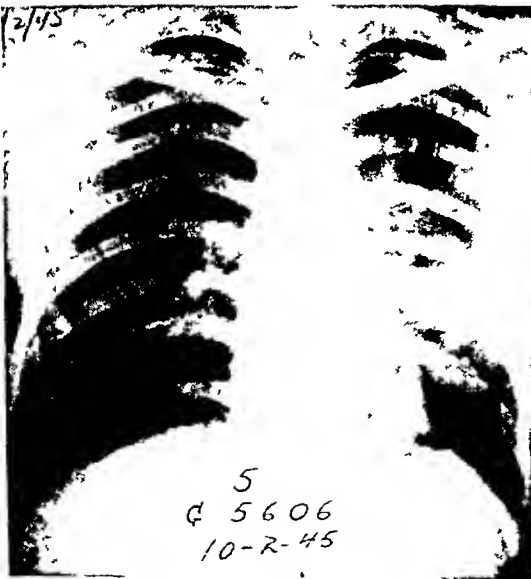
A. December 30, 1944. Shell fragment embolic from right femoral vein into right pulmonary artery, with infarction of right lower lobe.

B. January 13, 1945. Result 11 days after removal of shell fragment, ligature of anterior portion of terminal artery and resection of sloughing infarcted right lower lobe. Note marked cardiac enlargement due to opening of large femoral arteriovenous fistula when shell fragment broke loose.

C. February 9, 1945. Marked regression in size of heart 16 days after repair of defect of artery and vein.

A

B



C

D

FIG. 16—G-5606: Injured: December 17, 1944. Shell fragment wound left chest—retained foreign body. Débridement of wound and aspiration
A. & B. January 9, 1945. Foreign body in left bronchus and pulmonary artery visualized through bronchoscope, with bleeding around it.
C February 10, 1945 Result 22 days after left thoracotomy and removal, with suture of defects in pulmonary artery and bronchus.
D. March 14, 1945. Note clearing of infarction.

without incident from the right ventricular chamber. This is the single foreign body which did not exhibit an adhesive obliterative pericarditis.

MEDICAL THORACIC SECTION

A separate Medical Thoracic Section has performed a real service in supervising all general medical problems of diagnosis and treatment. The care of nutritional deficiencies, anemia and similar conditions, has been improved. The cardiologist and psychiatrist have lent valuable aid. The program of rehabilitation has been jointly shared. Individual instruction in breathing

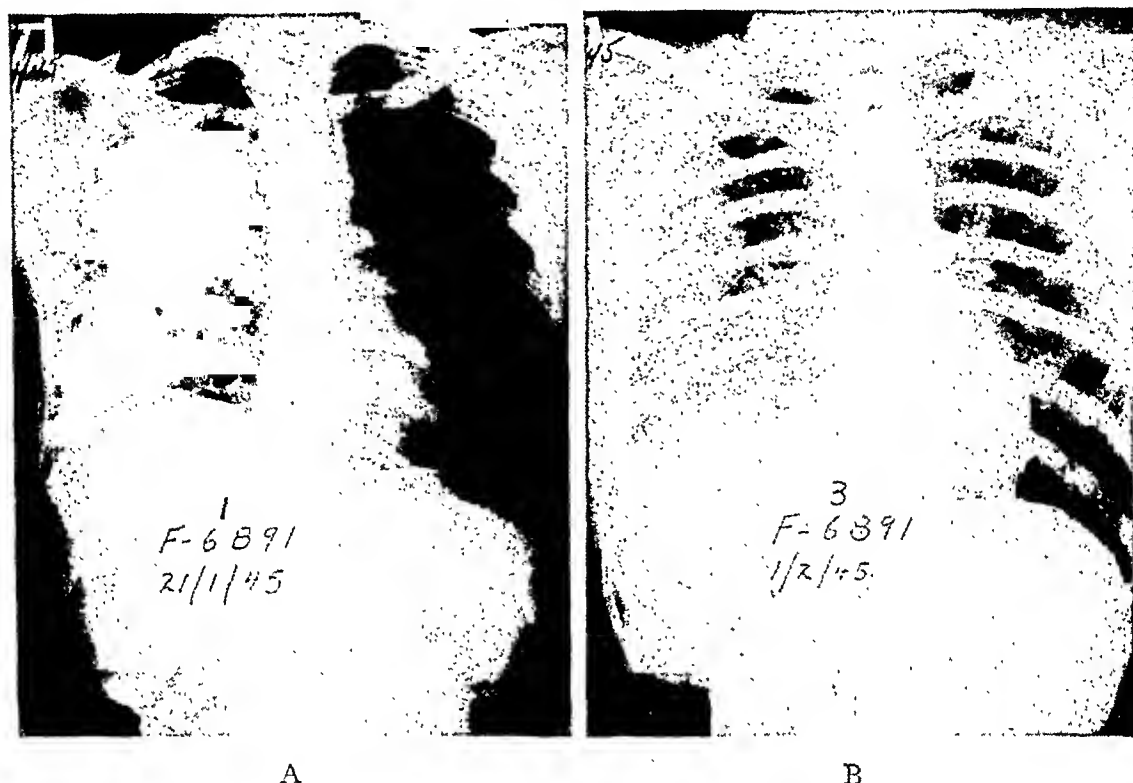


FIG. 17.—F-6891: Injured: December 4, 1944. Penetrating wound right chest.

- A. January 21, 1945. Shell fragment in wall of superior vena cava projecting into its lumen.
B. February 1, 1945. Result three days after removal and suture of defect in superior vena cava. E. K. G. showed marked left axis deviation:

exercises has been started soon after admission. They have been continued immediately after operation. The most extensive procedures, including those on the heart, have not prevented mobility out of bed in 24 hours. In about seven days, when surgical attention was no longer required, the patients have been routinely transferred to the Medical Section. The spirit of these wards has cultivated confidence in the ability to get well. The rapid change from the incurable patient idea to soldier status has been invaluable in continuation of rehabilitation. As vital capacity has gradually increased, general exercises, competitive games, and other activities, have been introduced. Marked improvement in weight, strength, anemia, physical and mental health has closely followed. It is certain that this activity has contributed most to the ability to return to duty.

RECOMMENDATIONS FOR THE CARE OF THORACIC CASUALTIES

All casualties would benefit if they could be treated throughout all echelons by medical personnel specially trained in the involved field. The comparative shortage of qualified thoracic surgeons has accentuated the lack of such an ideal situation. However, past mistakes may be noted and avoided in less desirable plans which must be substituted. The belief by some that thoracic exploration in the forward area is a "push-over" is indicative of an attitude which is not amenable to correction by written instruction. Mere survival cannot be accepted as a satisfactory measure of efficiency of thoracic operation. The record shows that innumerable and excellent results have been achieved by qualified thoracic surgeons with a mortality that is approaching *nil*. Except for patients facing immediate disaster, every surgeon should be prepared to accept his results as the product of his work. If he will adhere closely to the principles and, when indicated, restrict his activity to that consistent with immediate preservation of life and safe transfer to care of qualified thoracic surgeons, the best interest of all will be served.

Special significance must be attached to common surgical problems when they occur in thoracic casualties because they initiate mechanisms which not only immediately threaten life but also profoundly influence future course. Hemorrhage, wounds and infection assume importance peculiar to the thorax.

Although methods of treatment must conform to accepted standard principles, they often must be of a special type to be applicable and efficient. It is evident that when methods have failed for any reason, principles have been compromised. The following procedures have proven to be some of the practical and efficient methods which permit rigid respect of principles which must remain as the sound basis of treatment.

TREATMENT IN THE FIELD

Few changes in field treatment are advisable.

Packing and occasional ligation usually suffice for control of hemorrhage. If it does not cease, it cannot be adequately treated without surgery and hospitalization. During this interval the continued use of blood and plasma is justified but should be supervised by a medical officer, since shock from disturbed thoracic mechanisms may require attention more urgently than blood loss.

First aid for cardiorespiratory imbalance has been quite satisfactory. Immediate closure of sucking or open wounds with occlusive dressings or packing should be continued. The erect or semi-erect positions, with the injured side dependent, contribute to efficiency of respiration. After wound occlusion, increasing distress must be attributed to a combination of progressive blood loss, tension and hemothorax. Aspiration should be sufficient to relieve acute distress. High negative pressures should not be sought since tension or hemorrhage may promptly recur. Surgery before hospitalization should be preserved for the rare extreme emergency. It is best displaced by intensive conservative therapy and evacuation to the greater facilities in hospitals.

TREATMENT IN FORWARD HOSPITALS

Many observers concur in the appraisal of thoracic surgery in the Forward Hospitals. Much has been exceptionally well done but too much has been done by others not trained in this field. Mistakes can be avoided in the future by simple measures upon which all agree.

Every patient should be carefully examined and clinically evaluated. The general course and the response to each therapeutic procedure must be carefully noted. Thoracic examination even with laboratory aids has been a poor substitute.

With careful examination the nonoperative cases may be readily separated for early disposition. Experience has shown that tangential nonpenetrating wounds of the thoracic wall and clean penetration by rifle bullets or small shell fragments are frequently followed by only minimal intrathoracic reaction. Hemorrhagic pneumonitis, atelectasis and hemothorax have recovered often without specific treatment. Although some minor cases may return to duty, any with moderate symptoms and all those entering or transversing the thorax, regardless of clinical status, must be evacuated to the rear.

The remaining patients cannot be evacuated immediately because of the possible or urgent necessity of therapy. This does not imply routine surgical approach. Institution of care should proceed with some routine plan since priority cannot be established easily for any one of a number of lethal conditions.

HEMORRHAGE .

Continuing hemorrhage must be controlled. On the surface, or as a rapidly recurrent hemothorax, it should be easily recognized. Brisk bleeding from the thoracic wall has been more common than from the lung, where it usually ceases with pulmonary collapse. If packing or hemostatic ligatures fail, exploration under general anesthesia is indicated. The reaction to blood-loss replacement, oxygen and other measures in the absence of upset thoracic physiology is a good index of the necessity of operation.

CARDIORESPIRATORY FUNCTION

When patients fail to improve after control of hemorrhage, cardiorespiratory function must be investigated. Reestablishment of it is not only essential to life but also intimately related to future results.

Respiratory exchange cannot be adequate without a competent air-way. The virtues of correct position, postural drainage, cough, oxygen, intercostal nerve block, strapping and tracheotomy, should supplement bronchoscopy, which cannot always reach the peripheral lesions.

Sucking wounds, open wounds, wounds with severe rib damage, and wounds with retained large foreign bodies, are incompatible with good results, and often life, if treated only with packing or dressing. All should be meticulously débrided and closed securely in anatomic layers, leaving the skin open if desirable. Needless sacrifice of any tissue, especially ribs and periosteum,

should be avoided to permit easier and more secure closure. Wiring through drill holes is less painful than pericostal sutures. Unstable walls which embarrass respiration and early thoracic exercise and complicate secondary surgery can be prevented by attention to these details.

The continued presence of blood and air in the pleural space should not be tolerated. The most conservative measures which will keep the pleural space empty should be instituted immediately and persistently used to maintain this state. If this is done, the lung will expand to establish vital function at the same time that late complications are being reduced by obliteration of dead space, removal of fertile culture media and use of penicillin. At least 70 per cent of all patients with hemothorax, pneumothorax or hemopneumothorax will recover with such treatment.

A number will not exhibit progressive lung expansion or clinical improvement and clearing of roentgenograms. If the thorax is closed, recurrence must originate from defects persisting from initial injury. Methods which can establish stability and induce gradual intrapleural changes are needed. Closed drainage is essential. In recurrent pneumothorax with or without tension an air catheter through the second space anteriorly, or elsewhere, as necessary, has been quite satisfactory. It is more effective than aspiration or the flutter-valve in controlling expansion which favors healing of fistulae. Massive and recurrent hemopneumothorax has not done well with either aspiration or a single basal catheter. Poorly-placed tubes have become occluded by clotting, expanding lung or a rising diaphragm and, also, could not release air as long as fluid covered the tube. Under these circumstances a low basal tube for fluid should be used as a supplement to the air catheter. This tube should be larger, multiple-holed and inserted horizontally along the upper border of the costophrenic sinus. The use of two tubes has been justified by experience, and seems acceptable for theoretic reasons. As air and blood are drained from the pleural space, the relatively greater leakage of air from the lung will convert the hemopneumothorax to a pneumothorax, except for minimal residual sinus collection. Assured evacuation of air prevents tension and permits progressive expansion. Residual collections have been small and well-localized after the lower tube has ceased to function. Recurrent hemothorax can be drained by a single basal drainage tube. If pure blood rather than a thinning exudate is continuously obtained from the pleural space, the diagnosis of continuing hemorrhage requiring surgery must be entertained.

In using tubes, certain points are of importance. They should have multiple holes, be of adequate size and properly installed. A No. 16 F. catheter, inserted by a cannula just through the parietal pleura, has been satisfactory for air. A soft basal intercostal tube (1-1.5 cm.) has drained best when inserted horizontally, and fairly dependently, with regard for position of the patient, lung and diaphragm to prevent early shut-off. The rate of expansion can be controlled to promote healing of fistulae by increasing the depth of immersion in the drainage bottle. This should never be elevated. They should be retained until expansion obliterates the pleural space or until the system

ceases to work. Patency can be maintained without risk by irrigation with penicillin solution (250 units per cc.). Although retention beyond 48-72 hours should usually be unnecessary, penicillin has stretched this safe period to about seven days.

EXPLORATORY THORACOTOMY

More conservative measures should be abandoned in favor of exploration when definite reasons exist. Some gravely injured patients face disaster unless the conditions are promptly corrected. Arrest of hemorrhage, repair of chest wall, defects and closed drainage are the essential procedures. Many can be expected to come to secondary operation because primary surgery must be designed to relieve only the emergency. Other indications appear when conservative measures do not yield satisfactory progress. Although this surgery may be temporarily delayed, it should be done early to prevent serious late complications. Efforts should be directed to meticulous cleansing of the pleural space and sinus tracts; removal of devitalized tissue and foreign material, closure of fistula and plastic repair of residual pleural, pulmonary and other defects. After such exploration the lung should be completely expanded, the thorax drained with at least two closed tubes, and the bronchi cleared by bronchoscopy or suction. Local and parenteral use of penicillin should be routine.

ANESTHESIA

Proper anesthesia is of primary importance in any thoracic procedure. If cardiorespiratory function is deficient or if intrathoracic operation is contemplated, or a risk, only general anesthesia with endotracheal technic is permissible. Any failure to insure adequate control of respiration may lead to incomplete operation and poor results or death. Chances should not be taken with local or intravenous agents.

ABDOMINOTHORACIC INJURIES

Abdominothoracic injuries require routine early exploration. Thoracic approach has many advantages and can be supplemented by other incision, as necessary. The high incidence of late suppurative complications may be partially attributed to improper drainage and insecure closure of diaphragm. Imbrication with interrupted and nonabsorbable sutures is an excellent routine for diaphragmatic rents. Some large ones may require suture to the thoracic wall. The pleural space should always be drained by a basal tube at least. An air catheter may be added as necessary. The phrenic nerve should not be crushed. Liver damage must always be dependently drained through an adequate flank or abdominal incision. If transthoracic drainage is necessary, every effort must be made to separate the thorax from the subphrenic area. Left subphrenic drainage is rarely necessary. Foreign bodies in the liver requiring major additional incision for extraction should remain undisturbed. Others can be removed. Large liver lacerations can be effectively treated with penicillin-saturated gauze, muscle grafts or closure. These injuries will always

carry a high mortality but these simple measures may reduce the inordinately high rate of late sequelae which have been some of the most difficult problems encountered to date.

CARDIAC INJURIES

Cardiac and pericardial injuries which survive initial trauma usually present an hemothorax and hemopericardium. The latter may be unrecognized. These patients should not be operated upon with haste. Acute cardiac compression can be controlled often by subxiphoid aspiration. Unremitting hemorrhage requires emergency exploration and possible suture of the heart. Foreign bodies in the pericardium do not demand immediate pericardiotomy. They should rarely be removed early, except when the sac has been opened for other cause. Aspiration permits beneficial delay and recovery from the precarious state which cardiac trauma initiates. In the muscle they are best undisturbed unless necessary for the control of hemorrhage. Within the heart they should be disregarded. On exploration of any traumatized pericardium the virtues of 5 per cent procaine, adequate exposure, pleuropericardial and pleural drainage, must not be neglected.

Injury to great vessels usually is expressed as a rapidly recurrent hemothorax. After prompt control of bleeding, efforts must aim at repair of vessel walls rather than ligation. Foreign bodies in the walls can be removed and suture completed after adequate control of circulation by temporary and properly-placed hemostatic ligatures. Heparinization has not been necessary in a large group of such cases.

FOREIGN BODIES

Foreign bodies are usually not the concern of Forward Hospitals. When they are in the pleural space, they should be removed early. Operation for others may be delayed or be incident to exploration for other cause.

CHEMOTHERAPY

Chemotherapy has contributed greatly to the improved results in thoracic casualties. No comparative basis exists to permit expression of more than opinions. The oral use of sulfa-drugs has had no demonstrable ill effects, and may be continued. Insertion in wounds should be discontinued because it has often occasioned foreign body reactions without evident benefit.

Intrapleural penicillin appears to have been very useful. After each aspiration and exploratory thoracotomy, 40,000 units should be instilled. Results further justify the intramuscular use of 120,000 units daily for three to five days after operation of serious wounding.

EVACUATION

After emergency care has established stability, air evacuation to Thoracic Center holds the greatest promise. If for any reason evacuation must be slow, use of conservative measures, along the line, must be intensified. Emergency operation should be a rarity. At the onset of any indication for thoracic surgery, prompt transfer to a Center should be effected.

THORACIC SURGERY CENTER

REAR HOSPITALS

Hospitals between the forward area and the Centers should, except in rare emergencies, confine their activity to the use of conservative measures. All medical officers should be alert to recognize poor progress or other indications for surgical therapy. While many general surgeons could do much of this work, the records do not substantiate this as the policy of choice. Until such time as the principles are more widely disseminated and regarded, the greatest good rests in transfer of these cases to the Thoracic Centers.

THORACIC CENTERS

The procedures, as outlined, have given good results in this Center. They should be interpreted neither as the only, nor necessarily the best, methods

TABLE IV
DISTRIBUTION—28 ABDOMINOTHORACIC INJURIES OPERATED UPON AT THORACIC CENTER

(A) Right side—18 cases	Thoracic Center										Forward Area	
	Operations							Cultures			Procedure	
	Number	Thoracic Drainage	Decortication	Subphrenic Drainage	Repair Diaphragm	Foreign Body: Removal	<i>Staph. aureus</i>	<i>Strept. hem.</i>	<i>Clostridia</i>	Others	Thoracic Drain	Subphrenic Drain
Complication												
I. Thoracic suppuration.....	7	7	0	2		1	4		5		3	2
II. Subphrenic suppuration.....	7			7		1	2	3	4		1	2
III. Combined thoracic and subphrenic suppuration.....	4	2	2	4	2				4		1	0
Total.....	18	9	2	13	2	2	6	3	13	0	5	4
(B) Left side—10 cases												
I. Thoracic suppuration.....	6	1	5			1	3	1		1	1	0
II. Subphrenic suppuration.....	1			1		1	1				0	0
III. Combined thoracic and subphrenic suppuration.....	3	1	2	2	3		2	1			0	0
Total.....	10	2	7	3	3	2	6	2	0	1	1	0

that can be applied. Further survey of all results will give a sound basis for final evaluation. They have significantly lowered morbidity. There have been no deaths in 200 consecutive operative cases reported in this paper.

SUMMARY

The observations on 300 patients treated in a Thoracic Center are reported. Conservative measures have been quite effective in the early care of thoracic casualties. Proper use of minimal procedures in sucking wounds, hemorrhage and shock, has averted immediate death and permitted complete recovery in many patients. A small number have required emergency operation. Hemothorax, pneumothorax or hemopneumothorax have persisted frequently, and required further therapy. At least 70 per cent of them have recovered with repeated aspiration and chemotherapy. In the others, diverse

circumstances have led to progression. The failure to obtain and maintain early and maximal lung expansion has been associated with persistence, clotting and infection. Neglect of the implications and details of surgical care of extensive sucking wounds, bronchopleural fistulae and retained foreign bodies have aggravated the situation. Acute empyema, multiloculated hemothorax and simple or suppurative constrictive pleuritis have resulted. Decortication has been more widely needed than simple drainage. It is a formidable procedure but has reduced morbidity and carried no mortality.

Abdominothoracic injuries have had a high incidence of late complications. These have been universally suppurative and can be traced, in part, to improper thoracic and subphrenic drainage and insecure closure of the diaphragm. A

TABLE V
DISTRIBUTION OF ORGANISMS IN 200 OPERATIVE CASES

Diagnosis	<i>Staph. aur.</i>	<i>Strept. hem.</i>	<i>Clos- tridia</i>	Other	Total Cases	Total Positive Cultures	Comment
1. Acute empyema.....	5	6	4	6	14	14	
2. Constrictive pleuritis (simple).....	3	2	1	4	29	10 25%	Five positive cultures around foreign bodies
3. Constrictive pleuritis (suppurative).....	10	8	4	8	39	39	
4. Abdominothoracic injuries	12	5	13	1	28	28	All 13 <i>clostridial</i> cultures obtained from right-sided lesions
5. Foreign bodies (lung, pleura, med.).....	15	16	9	20	78	48 62%	
6. Foreign bodies (heart)...	4	4	0	0	20	8 40%	Around foreign bodies and from pericardium

multiplicity of extensive procedures have been required to cure these patients. Any success has been related to the possibility of repair or interposition of the diaphragm to separate the thoracic and abdominal components and permit individual treatment of each.

Foreign bodies have not been difficult. The majority have been asymptomatic and removed empirically by reason of size or location. Any tendency to induce late parenchymal changes has not been observed in a period which has been necessarily short. Elective operation for these have entailed neither mortality nor morbidity.

Some foreign bodies have been definitely associated with sequelae. Those in the pleura predisposed to empyema. Large irregular fragments have been frequently followed by fistulae, abscesses and delayed suppuration. All have been routinely removed without ill effect during operation for other cause.

The safety of surgical removal of foreign bodies from the heart and great vessels is established. This reported series of 20 has been increased to 30 successful operations, without serious complication and with no mortality.

Penicillin appears to be a most efficient agent. Its action is at least a plausible explanation of the results in the presence of so much suppuration.

A qualified anesthetist has been invaluable. Without gas, oxygen and

ether anesthesia, with endotracheal technic, and close supervision of the allied problems of circulation and respiration, much of this work would not have been possible. Routine postoperative bronchoscopy has yielded excellent results. Delegation of this to the anesthetist has been found highly satisfactory.

The rehabilitation of all thoracic patients has been most effective when total mobility has been obtained early.

Concentration in the hands of trained personnel has improved the treatment of thoracic casualties. In 200 consecutive cases definitive surgery has remarkably reduced morbidity and incurred no mortality. The greatest portion of improvement in results must be credited to the type of patient. He has been a young, previously healthy individual who has been able to face surgery with a minimum of risk.

CONCLUSIONS

The therapeutic problems of thoracic injuries fall into two basic groups: The first demand immediate attention to save life. They are concerned with the control of hemorrhage and the reestablishment of cardiorespiratory function. The second does not threaten life immediately, and some delay in treatment is permissible. They involve the early maximal restoration of normal anatomic and physiologic relationships. Operative and nonoperative measures are useful in both groups, but they are not mutually interchangeable. Conservative measures should be pushed to the limit when they can suffice. When they fail or are unsuitable, operative approach is indicated. Success will be greatest when familiarity with, and regard for, principles governs the application of methods. Since this has not been uniform, a wider dissemination of the principles and possibilities of this field of surgery is needed.

The American soldier has been the finest patient in the world. The manner in which he has borne all his misfortune has kindled a sense of pride which has made the care of him a privilege. It is good to be an American.

Note: The activities of recent months has increased the series to 314 consecutive operative cases. The breakdown of these conforms closely to the figures detailed in this report. No deaths have occurred.

THE MODERN TECHNIC OF THE LE FORT OPERATION

ROBERT TAUBER, M.D., F.A.C.S.

PHILADELPHIA, PA.

FROM THE GYNECOLOGIC SERVICE OF PROF. WILLIAM R. NICHOLSON, GRADUATE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

THE TREATMENT of a third-degree prolapse of the uterus is still a problem. The choice of the operation depends in a large measure on the condition of the uterosacral ligaments, the size of the uterus, the age of the patient, and whether matrimonial relationship is desired.

Of the several possible procedures the so-called modified Le Fort operation is the subject of the present communication.

The development of this operation dates from 1823, when Gérardin (Metz) had the original idea of resecting the lower portion of the anterior and posterior vaginal mucosa and then uniting the denuded portions to cure a third-degree uterine prolapse. But he never undertook the operation. Neugebauer (Warschau), in 1876, operated and published a case of uterine prolapse, according to Gérardin's method, though he resected a higher portion of the vaginal mucosa than Gérardin proposed. He gave the operation the name "elytrorrhaphia or colporrhaphia mediana" and reported, in 1881, 11 cases. Spiegelberg (Breslau), in 1872, used the same technic and Le Fort (Paris), in 1876, recommended this method for the treatment of uterine prolapse. The procedure is known in this country as the "Le Fort" operation and in the German literature as the "Neugebauer-Le Fort" operation. The first three cases operated upon by this method in the United States were reported 1881 by Berlin.

Many surgeons have used this procedure. The results, however, of the original Le Fort operation were not satisfactory and recurrences occurred. The plain resection of two symmetrical rectangular pieces of the anterior and posterior vaginal mucosa and the connection of the denuded areas proved insufficient. Many modifications (Adair and Phaneuf) were used in order to improve the results and to prevent recurrences. Most leading textbooks mention the operation but there are useful technical details not included in their description.

The causes of the recurrences have been almost universally the same: (1) The resected vaginal flaps were too small and consequently the lateral canals were too wide. (2) The approximated surfaces did not heal and partial separation occurred.

The numerous improvements of the operation result in the following technic, the main idea of which is a combination of four procedures: (1) Closure of a wide central portion of the vagina. (2) Formation of a suitable fascial support for the cystocele, the rectocele and the prolapsed uterus. (3) Formation of the inverted U-shaped canal. (4) Repair of the pelvic floor.

In the modern technic the resected flaps of the anterior and posterior vaginal mucosa are large and their shape is completely different the one from the other. The enlargement of the denuded area makes the diameter of the

U-shaped canal smaller.⁹ The difference in the shape renders it possible to continue immediately with the plastic of the pelvic floor, which is a very important part of the operation.³¹

OPERATIVE TECHNIC

Three points should be marked as the limits for the incision of the anterior vaginal mucosa (Fig. 1). Point 1 is in the midline, half a centimeter below the external urinary meatus. Points 2 and 3 form the end-points of the anterior transverse incision which is about three centimeters above the cervical opening.

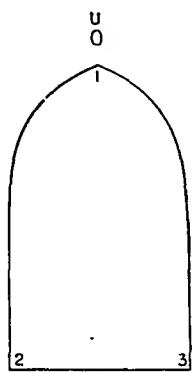


FIG. 1

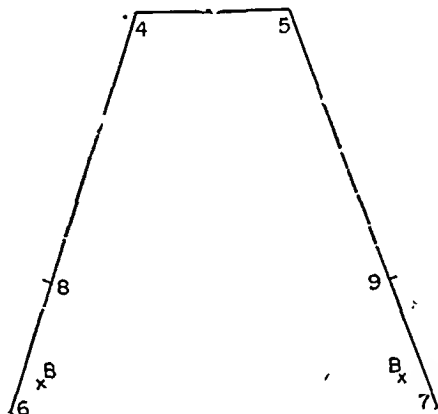


FIG. 2

FIG. 1.—Incision of the anterior vaginal mucosa. U is the external urinary meatus. Point 1 is half a centimeter below U. The transverse incision between Point 2 and Point 3 is three centimeters above the external uterine orifice.

FIG. 2.—Incision of the posterior vaginal mucosa. The transverse incision between Point 4 and Point 5 is three centimeters behind the external uterine orifice. Points 6 and 7 are at the border of the vaginal mucosa and the skin, close to the opening (B) of the Bartholin's glands.

The three points of the anterior flap should not be connected by straight cuts to form a triangle. It is better to make three-quarters of the lateral incisions parallel to the long axis of the uterus and the last quarter in a slight bow to the Point 1 below the urethra (Fig. 1). The resulting shape of the flap is frequently compared with a Gothic window or a snowshoe.¹ This flap of the anterior vaginal wall should be removed in one piece at once.

The shape of the resected portion of the posterior vaginal mucosa is completely different from the resected flap of the anterior vaginal mucosa. Four points have to be marked. Points 4 and 5 (Fig. 2) are the end-points of the transverse incision of the posterior vaginal mucosa, which is about three centimeters distant from the cervical opening. Points 6 and 7 (Fig. 2) are on the skin close to the opening of the Bartholin's glands.

The lateral cuts connect the Points 4 with 6, and 5 with 7, and give the posterior flap a trapezoid-shape (Fig. 2).

The idea of the different shape of the anterior and posterior flap is, that in forming the inverted U-shaped canal the Point 1 of the anterior incision (Fig. 1) will meet the Point 8 as well as Point 9 (Fig. 2) of the posterior incision in the midline. From this point, where the Points 1, 8 and 9 meet, runs

the balance of the posterior incision, Points 8 to 6 and 9 to 7, to the skin (Fig. 2). This part of the incision corresponds exactly with the usual angular incision made in the routine colpoperineorrhaphy. The advantage is, that, first, all unnecessary vaginal mucosa is removed; and, second, that the deep portions of the muscles can be reached to build a sufficiently supporting perineal floor. The end-points of the incisions at the skin, 6 and 7 (Fig. 2), can be connected by a slight bow, as used in the ordinary posterior plastic and, finally, the entire posterior flap is removed.

TECHNICAL DETAILS

In performing the transverse incisions near the cervix between Points 2 and 3 (Fig. 1), and between Points 4 and 5 (Fig. 2), care must be taken not to be too close to the external uterine orifice, otherwise the formation of the transverse canal below the cervix is impossible because the inverted vaginal mucosa would be too tight over the cervix.

The suturing of the vaginal edges in order to form the inverted U-shaped canal is one of the most important steps of the operation. A few rules for the canal sutures should be observed: (1) Only interrupted chromic catgut sutures, Nos. 1 or 2, should be used. (2) All knots must be on the inside of the newly-formed U-shaped canal, in other words, on the intact vaginal mucosa and not in the denuded area. This is necessary to unite the new edges of the vaginal mucosa by so-called inverted stitches. That means that the needle has to go first through the *posterior* vaginal mucosa *from the intact surface to the denuded area* and *then* through the anterior vaginal wall from the denuded area to the intact surface (Fig. 3). If not done in this way the intact tissue of the vagina would be brought together instead of the newly-formed wound edges and an exact healing would be impossible.

The direction in which the needle is passed through the vaginal mucosa is important in order to avoid a very disturbing tangling of the sutures. Figure 3 shows how to overcome this trouble. It is advisable in applying the sutures that the assistant at the respective side takes the end of the ligature in his hand before the needle passes the posterior wall and keeps the end of the ligature in his hand until the anterior vaginal mucosa is transfixed. These technical details help to avoid tangling of the sutures and allow an exact adaptation of the wound edges. In starting on the posterior wall, backhand stitches can be avoided and the technic will become much clearer and more exact.

In forming the U-shaped canal, the perivesical and perirectal connective tissue is approximated. Dead spaces and small hematomas, which cause failure in healing must be avoided. This is accomplished by use of No. 00 chromic catgut sutures, applied in an anteroposterior direction, passing first the perivesical and then the perirectal fascia. They should not be tied before a series of four to five sutures have been inserted. These stitches plicate the excessive tissue of the cystocele and rectocele.⁷ After a few canal-forming stitches through the vaginal wall another series of middle stitches should be applied.

After the whole canal has been formed, the entire edge of the anterior vaginal wall has been used up and Point 1 (Fig. 1) of the anterior incision will be forced to meet Points 8 and 9 (Fig. 2) of the posterior incision in the

midline. This is the vertex of the angle formed by the balance of the posterior incision, which is used for the following colpoperineorrhaphy. The flap of the posterior wall which is still present is now removed by a transverse cut which connects the Points 6 and 7 (Fig. 2). Instead of the transverse cut an angular excision of the perineum can be substituted, which allows a better muscle plastic of the perineorrhaphy.

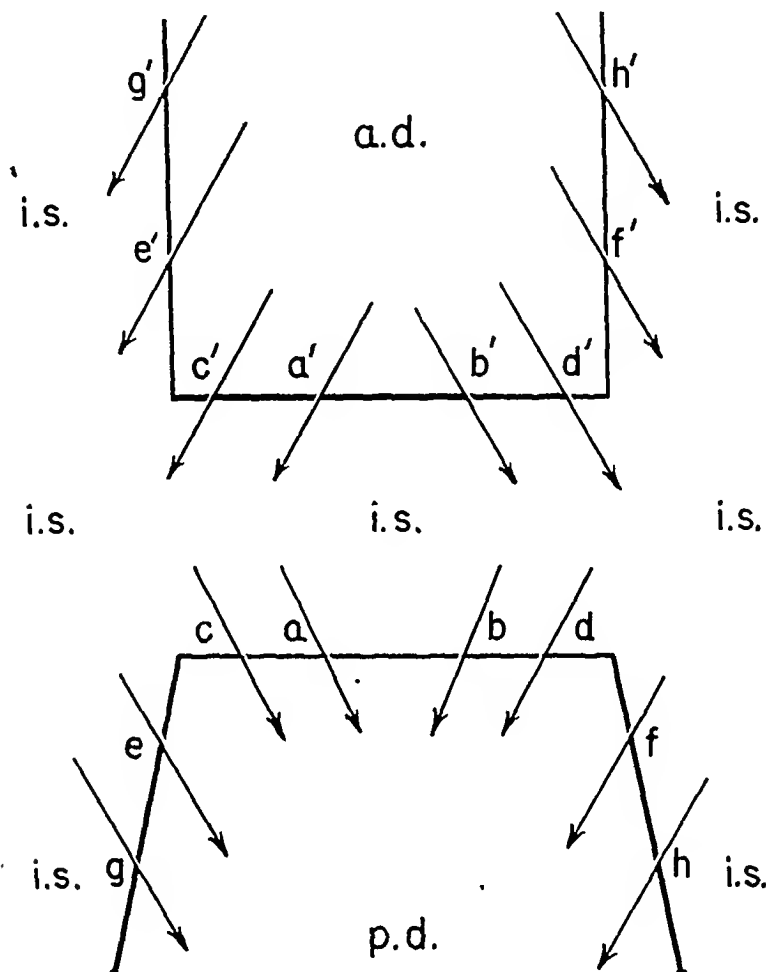


FIG. 3.—Direction of the canal-forming stitches aa', bb', cc' and so on. The needle has to pass first the posterior wall from the intact surface (i.s.) to the posterior denuded area (p.d.), and then the anterior mucosa from the anterior denuded area (a.d.) to the intact surface (i.s.). In this way the knots of the interrupted stitches will be on the intact surface and not in the denuded area.

CASE REPORTS

Case 1.—Mrs. H. D., age 60, has had four children. She complained of having a mass coming out of the vagina, causing severe difficulties in walking and sitting.

The vaginal examination revealed a mass as large as a man's fist, protruded from the vulva and lying between the thighs. The mass was covered by the inverted vaginal walls which were firm and dry. At the lower part of the mass was the cervix with the external os. No erosion or ulceration was present. The very small uterus was palpable between the vaginal walls. *Diagnosis:* Third-degree prolapse of the uterus and the vagina.

Operation.—The modified Le Fort operation was performed as described above.

The postoperative course was uneventful, and patient left the hospital on the 17th day. The examination on discharge showed a very good result.

Follow-up examination two years after the operation has shown an excellent result.

No bulging on bearing-down could be detected. Patient felt perfectly well and was free of complaints.

Case 2.—Mrs. J. S., age 66, has had three children. She complained of dragging pain in the back and pelvis which became worse when walking. She had the feeling that a mass comes out of the vagina, causing severe difficulties in walking and sitting.

The vaginal examination revealed a mass nearly as large as a fist protruded from the vulva and lying between the thighs. It was covered by the inverted vaginal walls which were firm and dry. At the lower end of the mass was the cervix with the external os. The fundus of the very small uterus was palpable between the vaginal walls.

Diagnosis: Third-degree prolapse of the uterus and vagina.

Operation.—The modified Le Fort operation was performed as described.

The postoperative course was uneventful, and patient left the hospital on the 15th day.

Examination on discharge showed a very good result. There was a slight discharge from the openings of the inverted U-shaped canal, due to the degeneration of the vaginal catgut sutures.

Follow-up examination after two years has shown an excellent result. Patient felt perfectly well and was free of complaints.

Case 3.—Mrs. C. G., age 65, has had two children. A supravaginal hysterectomy was performed 20 years ago. Patient complained of dragging pain in the back and pelvis which became worse when walking. She had the feeling that a mass comes out of the vaginal opening which made her unable to sit or walk. She wore a ring pessary for many years, which had to be removed because of local irritation.

Vaginal examination revealed a mass as large as a man's fist, protruded from the vulva and lying between the thighs. It was covered by the inverted vaginal walls which were firm and dry. There was no uterus palpable between the vaginal walls but there was a very small cervix on the lower end of the mass. *Diagnosis:* Complete prolapse of the vagina following abdominal hysterectomy.

Operation.—The Le Fort operation was performed in the modification as described above.

The postoperative course was uneventful, and patient left the hospital on the 14th day.

Examination on discharge showed a very good result. There was a slight discharge from the opening of the inverted U-shaped canal, due to the degeneration of the vaginal catgut suture. Irrigation through the U-shaped canal could easily be performed.

Follow-up examination after two years has shown an excellent result. No bulging on severe bearing-down could be detected. Patient felt perfectly well and was free of complaints. Bladder function and bowel movement normal.

Case 4.—Mrs. C. M., age 71, had had three normal deliveries. She complained of dragging pain in the back and pelvis and the feeling that a mass is coming out of the vagina causing severe difficulties in walking and sitting.

The vaginal examination revealed a mass as large as a fist protruded from the vulva and lying between the thighs. It was covered by the inverted vaginal wall which was firm and dry. At the lower part of the mass the cervix could be recognized by the opening in the center. The entire very small atrophic uterus was palpable between the vaginal walls. *Diagnosis:* Third-degree prolapse of the uterus, huge cystocele and rectocele.

Operation.—The Le Fort operation was performed in the modification as described above.

The postoperative course was uneventful, and patient left the hospital on the 17th day.

Examination on discharge showed a perfect healing. A slight discharge from the canals could be removed by irrigation of the U-shaped canal.

Follow-up examination two years after the operation has shown an excellent result. No bulging on bearing-down could be detected. Patient felt perfectly well and was free of complaints.

Case 5.—Mrs. J. G., age 51, has had two children. She complained of having a mass coming out of the vagina, causing severe difficulties in walking and sitting. The vaginal examination revealed a mass as large as a man's fist protruded from the vulva. After

replacing the mass it was expelled on slight bearing-down. At the lower part of the mass was the cervix with the external os, the fundus of the uterus was palpable between the vaginal walls. *Diagnosis:* Third-degree prolapse of the uterus, cystocele and rectocele.

Operation.—The modified Le Fort operation was performed as described above.

The postoperative course was uneventful, and patient left the hospital on the 17th day.

Examination on discharge showed a very good result. There was a slight discharge which could be removed by irrigation through the U-shaped canal.

Recently, I reexamined the patient. She has no complaints and feels perfectly well. No bulging on bearing-down could be seen.

DISCUSSION.—In the Cases 1, 2 and 4 the choice of the modified Le Fort operation was determined by the age of the patients (60–71), and that marital relations were no longer of importance. The youngest of this series, (Case 5) was 51 years of age. She was a widow, had a very small uterus and a complete relaxation of the uterosacral ligaments. Her general condition was not very good and, therefore, we decided to perform the Le Fort operation in the above described modified technic.

In Case 3 the choice of the modified Le Fort operation was easy. The absence of the uterus excluded consideration of hysterectomy as well as the interposition operation. There could be no better procedure for this case than the modified Le Fort operation.

A definite advantage of the operation is that there is practically no operative risk. The technic is not difficult, though it needs a certain skill to observe the mentioned technical details.

In favor of the operation is also the fact that the greater part of the entire procedure can be performed without any anesthesia. This may seem unbelievable, but experience has shown that the incisions and the removal of the anterior vaginal flap is completely painless even without local anesthesia.^{31, 32} The posterior vaginal wall can also be removed without pain by careful separation, especially in the region close to the cul-de-sac of Douglas. The perineorrhaphy, of course, needs local anesthesia. Considering that the operation is performed mostly on aged patients, the advantage of performing the largest part of the whole procedure without anesthesia cannot be overlooked.

In the presented cases (1, 3, 4 and 5), I performed the separation of the anterior vaginal flap without any anesthesia, and the patients did not complain of pain. The separation of the posterior flap was also done without anesthesia until the region of the cul-de-sac of Douglas was reached. In the Cases 1, 3 and 5 I could continue until the entire U-shaped canal was formed. Before the last stitches of the U-canal are applied I start routinely with the infiltration of the perineum and the lowest part of the labia majora. In Case 4 I had to infiltrate the posterior vaginal wall in the region close to the cul-de-sac of Douglas. Case 2 was done under general anesthesia because the highly nervous patient desired to be under anesthesia before entering the operating room.

I do not feel that the possibility of a later development of a carcinoma of the uterus should be considered as a contraindication to this valuable operation, because irradiation and operative treatment is still always possible and the open U-shaped canal would reveal any suspicious discharge or hemorrhage at any time subsequently. Moreover, the incidence of uterine carcinoma in women with atrophic uteri is indeed rare.¹

BIBLIOGRAPHY

- ¹ Adair, F. L., and DaSef, L.: *Am. J. Obst. & Gynec.*, 32, 218, 1936.
- ² Berlin, F.: *Am. J. of Obst.*, 14, 866, 1881.
- ³ Borrás, P. E.: *Bul. Soc. de obst. y ginec. d. Buenos Aires*, 22, 411, 1943.
- ⁴ Crossen, H. St., and Crossen, R. J.: *Operative Gynecology*. C. V. Mosby Co. St. Louis, 1938, p. 463.
- ⁵ Culbertson, C.: *Surgery of the Female Pelvis*. *Gynec. & Obst.*, Monographs, D. Appleton & Co. New York-London, 1923, p. 80.
- ⁶ Curtis, A. H.: *Textbook of Gynecology*. W. B. Saunders Co. Philadelphia, 1941, p. 438.
- ⁷ Dannreuther, W. T.: *Am. J. Obst. & Gynec.*, 43, 286, 1942.
- ⁸ Döderlein, A., and Kroenig, B.: *Operative Gynäkologie*. G. Thieme, Leipzig, 1924, p. 315.
- ⁹ Eustache, M.: *Bull. et Mém. de la Soc. de chir. de Paris*, 7, 428, 1881.
- ¹⁰ Gérardin, R.: *Memoire présenté à la Société médicale de Metz en 1823*. *Arch. générales de médecine*, Paris, 1825, p. 132.
- ¹¹ Hartmann, H.: *Gynécologie Opératoire*. Paris, 1911, p. 157. *Ann. de gynéc. et d'obst.*, 72, 351, 1916.
- ¹² Hegar, A., and Kaltenbach, R.: *Operative Gynäkologie*, Enke, Stuttgart, 4, 763, 825, 1897.
- ¹³ Hofmeier, M.: *Grundriss d. Gynec. Operationen*. Deuticke Leipzig, 1905, p. 185.
- ¹⁴ Hue, F. A.: *Annales de Gynécology*, Paris, 18, 40, 1882.
- ¹⁵ Jobert, de Lamballes: *Traité de chirurgie plastic*, quoted by Schwabe.³¹
- ¹⁶ Kelly, H. A., and Noble, B.: *Gynecology and Abdominal Surgery*. W. B. Saunders Co. Philadelphia-London, 1907, p. 63 & 382.
- ¹⁷ Kassmann, R.: *Allgemeine Gynecologie*. Berlin, 1903, p. 227.
- ¹⁸ Konrad, M.: *Wien. med. Wochschr.*, 47, 1133, 1157 & 1187, 1871.
- ¹⁹ Kraul, L.: *Berichte Über d. ges. Gynäk. & Geb.*, 37, 1, 1938.
- ²⁰ Kune, T. N.: *Engl. Med. Monthly*, Newtown, Conn., 2, 301, 1882-83.
- ²¹ Le Fort, L.: *La Lancette française*, 22, 174, 1877. *Bulletin générale de Therapeutic*, 92, 33, 1877. *Bulletins et Mémoires de la Société de chirurgie de Paris*, 3, 132, 1877.
- ²² Martius, H.: *Die gynäkologischen Operationen*. Thieme, Leipzig, 1937, p. 258.
- ²³ Müller, E.: *Gaz. Méd. de Strasbourg*, 3, 68, 1883.
- ²⁴ Mundé, P. F.: *Minor Surgical Gynecology*. New York, 1885, p. 533.
- ²⁵ Neugebauer, L. A.: *Pamiętnik Towarzystwa lekarskiego Warszawskiego*, 8, 227, 1868. *Zbl. f. Gyn.*, 5, 3 and 25, 1881.
- ²⁶ Panas, M.: *Bullet. et Mém. de la Soc. d. chirurg. de Paris*, 5, 188, 1879.
- ²⁷ Phaneuf, L. E.: *Am. J. Obst. & Gynec.*, 30, 544, 1935.
- ²⁸ Pinzani, E.: *Riv. di obstet. et ginecol. Torino*, 2, 257, 1891.
- ²⁹ Reifferscheid, K.: In Halban-Seitz: *Biologie & Pathologie d. Weibes*, Urban & Schwarzenberg, Berlin-Wien, 3, 679, 1928.
- ³⁰ Rice, A.: *Maryland Med. Jour.*, Baltimore, 4, 796, 1883.
- ³¹ Schwabe, L.: *Mon. f. Geb. & Gyn.*, 44, 396 and 468, 1916.
- ³² Sokoloff, A.: *Annales of Gyn.* Paris, 21, 13, 1884.
- ³³ Spiegelberg, O.: *Berlin. kl. Wchschr.*, 1872, p. 262.
- ³⁴ Taft, C. E.: *Am. J. Med. Sc.*, Philadelphia, 98, 128, 1889.
- ³⁵ Tischler, H.: *Zentr. f. Gyn.*, 66, 916, 1942.
- ³⁶ Ulrich, P.: *Compt. rend. Soc. Franc. de gynéc.*, 9, 179, 1939.
- ³⁷ Veit, J.: *Handbuch d. Gynäkologie*, II. Ed. 1, 328, 338 and 357, 1907.
- ³⁸ Weibel, W.: *Die gynäkol. Operationstechnik d. Schule E. Wertheim*, Springer, Berlin, 1923, p. 153.
- ³⁹ Winkel, F. K.: *Lehrbuch d. Frauenkrankheiten*, Hirzel, Leipzig, 1890, p. 359.
- ⁴⁰ Wyatt, J.: *J. of Obst. & Gynec. of the Brit. Empire*, 22, 266, 1912.
- ⁴¹ Zankarol: *Bullet. et Mem. Paris*, 5, 707, 1879.

COMPOUND INJURIES OF THE KNEE JOINT*

STUDY I—TREATMENT OF NONINFECTED KNEE JOINTS

JOE M. PARKER, M.D., AND JOHN J. MODLIN, M.D.

St. Louis, Mo.

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, AND BARNES HOSPITAL,
SAINT LOUIS, MISSOURI

DURING THE TWO AND ONE-HALF YEARS in which the armed forces were engaged in active warfare, first in the Mediterranean Theater and later in the European Theater, many well-crystallized ideas about the surgical management of the wounded were developed. The program of early reparative surgery, as envisioned by Colonel E. D. Churchill, is, without doubt, one of the major contributions to come from the present conflict.

The surgery of wounds of the knee joint is an outstanding example of a field where clear, concise ideas of the proper type of surgical care have evolved. The early care of these penetrating and perforating injuries is now well-standardized. The joint must be opened widely and explored in order to remove all destroyed and devitalized cartilage and bone. The synovium is then closed, and penicillin is instilled into the joint. The skin is left open in the Forward Hospitals.

The Office of the Surgeon-General has recognized the need for early, thorough exploration of compound injuries of the knee. Technical Bulletin No. 147, published in March, 1945, states: "The wound of the soft-part is excised and the bone and cartilage damage assessed through incisions that provide complete exposure. Comminuted fragments of bone and cartilage are removed from the joint and a careful search made for foreign material." Thompson, Cassebaum, and Stewart recorded the experiences of an Evacuation Hospital in treating war wounds of the knee. Their observations were based on 172 penetrating injuries of the knee, 131 of which were subjected to formal, exploratory arthrotomy. We received many of these patients and know that the results were excellent.

With the accepted, early treatment of knee injuries by exploratory arthrotomy, the patient is given the best opportunity to escape the consequences of a suppurative arthritis. Furthermore, the later function of the joint is best assured by the early removal of all loose and foreign bodies. It should be emphasized that the after care of these wounds is very important. Much of the future function depends on the proper management of such patients at the Base Hospitals. Assuming that the knee wound has been cared for primarily in the Forward Hospital, the wounded man is usually transportable to the Fixed Hospitals after the effects of the anesthetic have worn off. Actually, he reaches the Base any time between the second and eighth day after wounding. The authors were concerned with the after care of these patients in the Base Hospital.

* From the 21st General Hospital (Washington University Unit).

During the 35 months spent in Africa, Italy and France,* over 300 compound injuries of the knee joint were seen and treated. Accurate statistics are available on 244 cases seen in Italy and France. Almost all these patients had received their primary care in the Evacuation Hospital.

Historical.—During the early part of the African campaign, the lines of evacuation were long and complicated, so that the majority of the patients were seen late after wounding. By the time the occasional patient with an infected knee joint reached the Base, a pyarthrosis had already developed. Unfortunately, no accurate figures are available on the penetrating wounds seen during the African campaign. In general, however, the initial surgery on penetrating wounds of the knee joint during this campaign consisted of the débridement of the wound, removal of the foreign body, and closure of the synovium. Some hospitals elected formal, exploratory arthrotomies, with closure of the synovium, even at this early date, but our records are too inadequate to draw any conclusions about the surgical principles employed in the Forward Hospitals. At the General Hospitals, the advantages of secondary suture of wounds were just being realized, and few knee wounds were actually sutured.

Septic joints with pyarthrosis were treated by bipatella incision, removal of the foreign body, irrigation of the joint space, and immobilization in a plaster hip spica. The synovium was held open by a pack which extended to, but not into, the joint. These patients usually had a stormy course and showed weight loss and other signs of chronic suppuration.

During the Italian campaign the management of wounds was changed radically. The program of secondary suture proved to be basically sound. Revolutionary advances were made in the management of soft-tissue injuries, but even greater was the advance in the methods of handling wounds of the knee joint. Whereas treatment of wounds early in the war was passive, and consisted principally of immobilization in plaster to avoid spreading infection, the program in Italy was changed to an active one, designed to control and eliminate infection and to restore function as early as possible. In the care of knee injuries, the early restoration of function is particularly important in order to avoid muscle atrophy and joint adhesions.

During the months of static warfare on the Cassino front in Italy, the Forward Hospitals reached a degree of excellence in the performance of débridements that has not since, in our opinion, been duplicated. The clean surgical wounds seen at the Base were most suitable for closure, and the entire program was facilitated. The value of routine, early arthrotomy became evident, but the procedure was not universally accepted during the early part of the Italian campaign.

The widespread use of penicillin as an aid in combating wound infection dates from the Spring of 1944. With the introduction of this new chemotherapeutic agent, the approach to reparative care of all types of wounded became

* The 21st General Hospital operated in North Africa from January to November, 1943, in Italy from January to September, 1944, and in France from October, 1944, until September, 1945.

more active. The conservative attitude toward treatment of knee joints with complicating infection changed to a more aggressive surgical approach. This viewpoint will be presented in Study II, based on this same series of 244 cases. The present paper is concerned with the early care of uninfected compound injuries of the knee joint. Although the conclusions are based on experience with battle injuries of the knee, they are also applicable to injuries of the knee seen in civilian surgery.

Care of Joint Injuries at the Base Hospital.—When received from the Forward Hospital, the patient with an adequately treated wound of the knee is comfortable, although he may have some fever if the period since wounding is short. He has had the benefit of arthrotomy, the joint has been débrided, the synovium closed, penicillin injected locally, the wound dressed, and the extremity immobilized in a long leg plaster encasement or Tobruk splint. A hip spica is preferred in the presence of severe bone injury. After correction of secondary anemia, and with the continuation of parenteral penicillin therapy, the patient is taken to the operating room, where facilities are available for formal arthrotomy. The plaster and dressings over the wound are removed. It is important that the original dressing should not be changed until this time, as repeated dressing of the wound leads only to secondary contamination and suppuration. If penicillin is instilled repeatedly at the Forward Hospital, it should be done without disturbing the dressings over the wound proper. After removal of the dressings in the operating room, the knee is inspected and tested for increased fluid, and most important, tested for pain on motion of the joint. The patient must necessarily remain awake during this portion of the procedure. The uninfected knee will have a small range of painless motion, whereas the infected knee joint is painful to even minor degrees of motion. It must be pointed out, however, that excessive ranges of motion, even in uninfected joints, will be painful. The patient is then anesthetized. If fluid is present, the joint is aspirated, the fluid examined grossly, and specimens taken for smear and culture. Gentle irrigation with saline through the aspiration needle is performed and the character of the returning fluid is carefully noted. The infected joint with leaking synovium will be apt to discharge flecks of purulent material with the irrigating fluid. If definite indication for arthrotomy exists, it should be done without delay, and with the aid of a pneumatic cuff tourniquet in order that the visualization of the joint be unimpaired. Usually, the joint which has received proper care in the forward area will need no further intra-articular surgery. Ten or twenty thousand units of penicillin in 10 to 20 cc. of saline are instilled into the synovial cavity. The skin, left unsutured in the Forward Hospital, is closed by simple suture. Systemic penicillin consisting of 25,000 units every three hours is continued from the time of admission to the Base until the knee wound is healed.

Immobilization.—The ordinary uncomplicated knee injury is usually immobilized in extension in a Tobruk splint. The principle of traction as well as immobilization is utilized by this type of splinting. Suppurating knee joints are immobilized in plaster hip spicas. However, it would seem that the type of

immobilization is not as important as the operative procedure in attempting to arrest the suppurative process within the joint. The real victories over infected joints rest in thorough exploration of the joint and removal of the cause or causes for suppuration.

The uncomplicated knee joint may require a second local instillation of penicillin, but usually the single instillation at the time of secondary suture is considered adequate. If indication for other injections arises, these may be done through a window in the encasement. The ordinary case without severe fracture is immobilized for about five to seven days after operation at the Base. Those cases where complication has occurred should receive daily local instillations of penicillin until the effusion has subsided and the temperature is receding. The systemic use of penicillin is continued also. Cases which respond favorably will generally show marked improvement in two or three days, the effusion subsiding gradually. The amount of periarticular swelling is sometimes surprising and becomes evident as joint effusion disappears. In the absence of major bone or soft-tissue damage, the plaster encasement is removed and gentle motion is started a few days after symptoms have subsided. No immobilization is used thereafter.

There is a minimal period during which the patient with a wound of the knee joint should be followed at the Base, and during which he should be considered nontransportable. This period is about three weeks in the average case. During this time, the skin should be closed, and quadriceps exercises and motion of the knee started. Evidence of suppuration or other complication, such as serious quadriceps atrophy or delay in moving the joint, is sufficient indication to prolong hospitalization in order to explore the knee or to supervise rehabilitation.

The keynotes in the after care of clean wounds of the knee are: First, the initiation of proper exercises as early as the first day after secondary suture of the skin to prevent quadriceps atrophy; and, second, the early mobilization of the joint to prevent the formation of adhesions that would restrict the range of motion. The latter is very important where the synovium has been destroyed at its lateral and medial reflections. For these reasons, the thoroughness of the initial care, aimed at preventing suppuration and smoothing articular defects, is probably the one most important phase in the proper care of compound injuries of the knee. It is only in those knee joints that have been properly cared for in the Evacuation Hospitals that early motion can be instituted.

Incidence of Complicating Fractures.—Bone injury was recorded in 168 of the 244 penetrating and perforating injuries of the knee. Forty-four of the entire series, or 18 per cent, were severe comminuted fractures of one or more condyles. Fracture of the patella occurred in 49 of the 244 cases, an incidence of 20 per cent. Thirteen of the series of 49 fractured patellae had had primary excision of the patella in the Forward Hospital. One patient had had partial excision of the patella at the Evacuation Hospital. At the time of reparative surgery, three more of the fractured patellae were excised, and the above mentioned partial patellectomy was completed.

COMPOUND INJURIES OF KNEE JOINT

TABLE I

	No. of Cases	Percentage
Total compound injuries of the knee joint.....	244	100
Total number of wounded, with bony injury.....	168	67
Total number with severe comminuted fractures.....	44	18
Total fractures of the patella.....	49	20
Fractures of the patella treated by primary excision.....	13	
Fractures of the patella treated by secondary excision.....	4 (1 exc. comp.)	
Total fractures treated by patellectomy.....	17	7

Severely comminuted fractures of the patella with irregularity of the articular surface should be treated by total patellectomy in order to minimize the later development of traumatic arthritis and to prevent infection. If a major fragment of the patella remains as a single piece with good articular surface, it may be possible to leave this segment in place, after removing the comminuted fragments. This may then be secured to the ligaments by wire sutures, if necessary. Experiments by Cohn indicate that total patellectomy is to be avoided when possible. The patella or portion of the patella is left only when the under surface of the part remaining is perfectly smooth. Many fractures of the patella are incomplete. Curettage of the fractured area and débridement of the injured tissue about it may leave almost the entire articular surface of the patella intact. Infected comminuted bits of the patella were curetted in four of the 49 fractures in this series.

If the roentgenograms are not decisive, the under surface of the patella should be felt with the gloved finger at the time of reparative surgery or secondary suture. This is to be done even at the risk of contaminating the joint by going through the wound to reach it.

In a large majority of cases, bone injury to the condyles is minor in nature, consisting of either penetrating injuries of bone, chip fractures, or incomplete fractures. On the other hand, the seriousness of the injury is not to be minimized in view of the danger of suppuration in the joint. The usual injury involves either the medial or lateral condyle of the femur, because the surface exposed is much greater. At arthrotomy, with adequate exposure, the irregular defect in the condyle is evident. The foreign body may project above the surface, embedded in the bone, or the elastic articular cartilage may close over the defect and hide the missile. In every instance, the missile should be removed when operative removal is not difficult. Sometimes, the missile will have passed up into the marrow cavity and usually it does not reflect good judgment to attempt recovery in such cases. After extraction of the metal, the edges of the defect are irregular and must be thoroughly smoothed and trimmed. Loose pieces of articular cartilage may interfere with the future function by doubling outward into the joint to become trapped between the tibial and femoral condyles. It is very important for future function as well as for the control of early infection, that the joint be inspected for loose particles. The defect in the condyle should be carefully prepared so that the edges are smooth and no tags of cartilage remain.

The severely comminuted fracture of the knee presents a serious problem at times. These wounds may be produced by either bullets or shell fragments.

The outlook is more serious in the latter. None of the four bullet wounds of the knee with marked degree of comminution developed a suppurating joint. There were 35 severely comminuted fractures secondary to wounding by shell fragments, and of this number, 12 patients developed uncontrolled infections of the knee joint. If the joint does not become infected, one can either use skeletal traction to avoid shortening of the extremity, or immobilize the joint in plaster hip spica to await solidification of the fragments. The shattered joint with irregular surface will probably require fusion at some later time.

The joint that is open as a result of the loss of soft-parts is also a serious problem. If the soft-parts are avulsed to such an extent that the joint cannot be closed, there is usually bone loss as well, and saving the joint is useless. If, however, there is loss of soft-parts with preservation of the bony and cartilaginous structures, prevention of infection is desirable, and a plastic procedure should be tried in order to try to close the joint space. In ten cases of the present series, there was loss of soft-tissues to such an extent that closure of the joint by simple suture was not possible. In five of the ten cases plastic closure was attempted. (The remaining five cases were damaged beyond repair.) This can be done either by swinging a wide-base pedicle flap over the soft-tissue defect of the joint, or by undercutting a bridge of skin, leaving it attached at both ends and advancing it over the defect. In two cases of the five the results were excellent and infection, otherwise inevitable, was avoided. A third patient had some drainage from beneath the flap which was thought to be from an osteomyelitis of the femoral condyle. He was afebrile when evacuated and his final result is not known at this time. Two cases must be regarded as failures, as both joints continued to drain along the borders of the flap. Flap closure is certainly to be tried in all those cases where enough of the bony parts remain to warrant an attempt to save the articulation. Such flap procedures are probably best done in the Forward Hospitals at the time of débridement. The delay in reaching definitive surgery is sometimes so great that irreparable damage is done to exposed articular surfaces before the joint is converted into a closed cavity.

The Italian and French campaigns have afforded an excellent opportunity to study the merits of routine early arthrotomy. During the early phase of the Italian campaign, 99 compound injuries of the knee joint were treated. Of these 99, only 32 had been subjected to formal arthrotomy at the time of initial care. In 60 cases, either débridement alone had been done, or, in some few cases, the foreign body had been considered small enough to leave in, or adjacent to, the joint. The records in the remaining seven patients are not clear.

With the invasion of Southern France, Colonel F. B. Berry, consulting surgeon to the 7th Army, directed that all wounds of the knee joint be subjected to formal arthrotomy. This directive was based on the experiences gained in Italy. The improvement in results was striking. One hundred and forty-five compound injuries of the knee were treated in France. Ninety-five of these had been subjected to complete exploration of the joint. The records in six other patients were inadequate. Forty-three patients had not been subjected to formal arthrotomy. (As patients reached us from other than the 7th

Army, the incidence of wounds débrided without arthrotomy increased.) The incidence of suppurating knee joints in the Italian series was about 16 per cent. In the French series, the over-all incidence was 9.6 per cent. However, the significant difference rests in those cases which were found to be septic on admission and which were amenable to secondary débridement of the joint. Of the 15 cases subjected to secondary arthrotomy as described in Part II, 12 were in the Italian series. Eleven of the 12 had not been subjected to formal arthrotomy in the Evacuation Hospitals. Of the three septic cases seen in France, and thought to be operable, all had been given the benefit of formal arthrotomy as part of the primary care. The reason for suppuration in these three cases was believed to be inadequate surgery. Suppuration in those joints with relatively minor cartilaginous and bony damage if left unchecked, is a much greater catastrophe than suppuration in a joint which will probably be nonfunctional due to severe fracture and irregularity of the joint surfaces. The significant difference between the series of routine, early arthrotomy and that of débridement of the soft-parts or simple removal of the foreign body lies in the reduced rate of infection in those cases where bony damage is minor and where preservation of a functioning joint is assured if infection can be circumvented.

Finally, a word should be said about the wounding agent. Table II shows the relative percentage in the present series:

TABLE II		
	Number	Percentage
Wounded by shell fragment.....	188	77
Wounded by small arms.....	44	18
Wounded by questionable agent.....	12	5

It is significant that 27 of the 28 knees that were septic on admission were the result of shell fragment wounds. The one septic bullet wound in the series as shown in the last table of Study II, is open to question. One must logically conclude that the highly shattered knee joint caused by a bullet wound should be treated conservatively, since the probability is that the joint will not become infected. On the other hand, the minor degrees of bone injury secondary to bullet wound require arthrotomy, not so much to avoid infection as to assure later function of the joint by removing loose and partially detached bone and cartilage from the joint.

SUMMARY AND CONCLUSIONS

1. Results of the surgical care of 244 compound injuries of the knee joint are presented.
2. The history of the evolution of a standardized program of reparative surgery in these cases is given.
3. Details of the surgical approach to the noninfected wound of the knee joint are outlined, with stress on the local and general use of penicillin.
4. The importance of the detection of early suppurative arthritis of the knee should be emphasized and the value of the diagnostic sign of pain on motion of the injured knee is stressed.

5. Early mobilization of these injuries is necessary in order to prevent joint and quadriceps atrophy, as well as restricted motion.

6. The high incidence of patellectomy in this series (35 per cent of patella fractures) is thought to be justified in view of the possibility of subsequent infection or traumatic arthritis.

7. The lowered incidence of sepsis treated in this hospital during the French campaign is believed to be convincing evidence of the value of the surgical program outlined.

REFERENCES

- ¹ Churchill, E. D.: Surgical Management of the Wounded in the Mediterranean Theater at the Time of the Fall of Rome. *ANNALS OF SURGERY*, 120, 268, 1944.
- ² Cohn, B. N. E.: Total and Partial Patellectomy. *Surg., Gynec., and Obst.*, 79, 516, 1944.
- ³ Thompson, J., Cassebaum, W., and Stewart, C.: Early Management of Penetrating Wounds of the Knee Joint. *Bull. U. S. Army M. Dept.* 1946—5: 439-44.
- ⁴ War Department Technical Bulletin, Medical No. 147: Notes on the Care of Battle Casualties. March, 1945.

(To be continued)

THE TREATMENT OF PERIPHERAL NERVE INJURIES COMPLICATED BY SKIN AND SOFT TISSUE DEFECTS

CAPT. STANLEY E. POTTER, M.C., AND MAJOR EDMUND J. CROCE, M.C.

HALLORAN GENERAL HOSPITAL

STATEN ISLAND, N. Y.

THE NECESSITY for early surgical intervention in peripheral nerve injuries is now fully appreciated by the military neurosurgeon. Earlier in the war, concomitant injuries to the bones and soft parts received major consideration; reconstructive neurosurgery was instituted at the completion of bone healing, reconstructive bone surgery, and major plastic procedures.

When the Neurosurgical Center was organized at this hospital, the complicated problem of combined orthopedic-neurosurgical cases was recognized, and a subsection was created for the treatment of these cases. The expeditious treatment of patients in this subsection has proven its value; methods of approach and results are soon to be published.

The handling of neurosurgical cases with associated soft-part damage and loss of skin has presented similar difficulties. The patient-load in this category probably does not warrant the creation of a special subsection; however, the need of a plastic surgeon at a Neurosurgical Center is apparent.

The transfer of neurosurgical patients to Plastic Centers for preliminary surgery postpones nerve repair. Such plastic repair is often compromised by the neurosurgeon and an excellent cosmetic result jeopardized. Certain complicated plastic repairs requiring tube construction can best be handled at a Center, and delay in nerve repair has to be accepted unless preliminary neurosurgery can be done and split grafts utilized as a temporary measure.

However, the rotation of flaps and the construction of pedicle flaps can often be done at the time of nerve repair. Thus, the patient is submitted to but one procedure, and his nerve repair is not postponed. The prolongation in operating time is not a major consideration since local anesthesia is possible in most nerve repairs and in the smaller flaps. Thus far we have not used general anesthesia during the neurosurgery.

The first seven cases of a series have been completed. The neural lesion has been treated by accepted methods and an assay of regeneration is not pertinent to this paper. However, we believe that our experience in the combined management might be of interest to those confronted with these problems.

Scarred skin or split-thickness grafts necessarily mobilized in surgical procedures for restoration of nerve function often become ischemic, thus endangering the underlying neurosurgical repair and requiring secondary plastic procedures. As a prophylactic measure, these areas of doubtful vitality are excised at the completion of the neurosurgical procedures when the skin defect is covered by a pedicle flap. For defects of the upper extremity the pedicle is

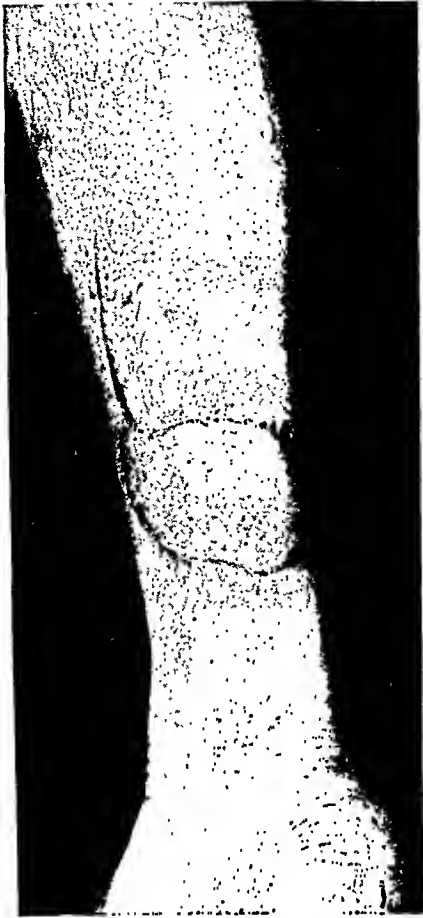


FIG. 1.—Case 1: Postoperative photograph of medial aspect of right leg showing healed full-thickness graft.

raised from the trunk. Since the suture of nerve defects often necessitates immobilization of the upper extremity in a varying degree of flexion, the donor site is sometimes on the chest wall. If circumstances allow, it is better placed on the anterolateral aspect of the abdomen where the skin is loose, where there is more subcutaneous tissue, and where the defect remaining after raising the graft may often be closed primarily without distortion of topography.

Defects of the lower extremity have been covered by pedicle grafts raised from the other lower extremity. Here again, immobilization in flexion often limits the choice of the donor site. It often becomes necessary to use the posterior aspect of the upper or middle thigh, resulting in moderate postoperative discomfort for several days. The use of this area as a donor site makes it possible, however, to close the defect primarily, as in the trunk, whereas a similar area on the calf would require a split-thickness graft.



FIG. 2

FIG. 2.—Case 2: Preoperative photograph of medial aspect of right ankle showing split-thickness graft overlying scar tissue.



FIG. 3

FIG. 3.—Case 2: Postoperative photograph of medial aspect of right ankle showing healed full-thickness graft.

PERIPHERAL NERVE INJURIES

A preliminary survey and examination of each case is done jointly by the neurosurgeon and plastic surgeon. The latter decides upon the type of plastic procedure desirable, instructs the neurosurgeon in the pattern of scar removal,



FIG. 4

FIG. 4.—Case 3: Operative photograph showing skin defect due to excision of split-thickness graft and scar tissue. The neurorrhaphy has been completed, and the sutured nerve lies exposed.



FIG. 5

FIG. 5.—Case 3: Postoperative photograph of the medial aspect of the left ankle showing the healed full-thickness graft.

and advises in the placing of the neurosurgical incision at the angles of the skin defect. Possible posturing of the extremity necessitated by the nerve repair is considered.

The neurosurgeon initiates the surgery under local anesthesia. The cutaneous scar or split graft is excised and the incision extended to permit of adequate exposure. The nerve is then repaired in the usual manner. It is

sometimes possible to transplant the suture site from the graft area (Fig. 7). If this is not feasible, it may be placed in a fresh muscle plane. We have not employed a tantalum sleeve in these cases; however, if the suture remains in a



FIG. 6.—Case 4: Preoperative photograph of right elbow. There is an extensive scar in large part immediately overlying bony tissue. A split-thickness graft had been utilized to secure early healing.



FIG. 7.—Case 4: Operative photograph showing pedicle graft in process of being sutured to the skin defect following excision of scar and split-thickness graft. The ulnar nerve has been transplanted anterior to the area of the pedicle graft.

moderately scarred bed at the site of the graft, a sleeve might be used. This should not be placed so as to underlie a suture line at the edge of the graft.

The recipient defect is carefully measured, and a gauze pattern is made with methylene blue. The outline of the pedicle graft is drawn with the dye by the aid of the pattern. In determining the length of the pedicle, due allow-



FIG. 8.—Case 4: Postoperative photograph of posteromedial aspect of right elbow showing healed full-thickness graft.



FIG. 9.—Case 4: Postoperative photograph of the trunk showing healed donor site.

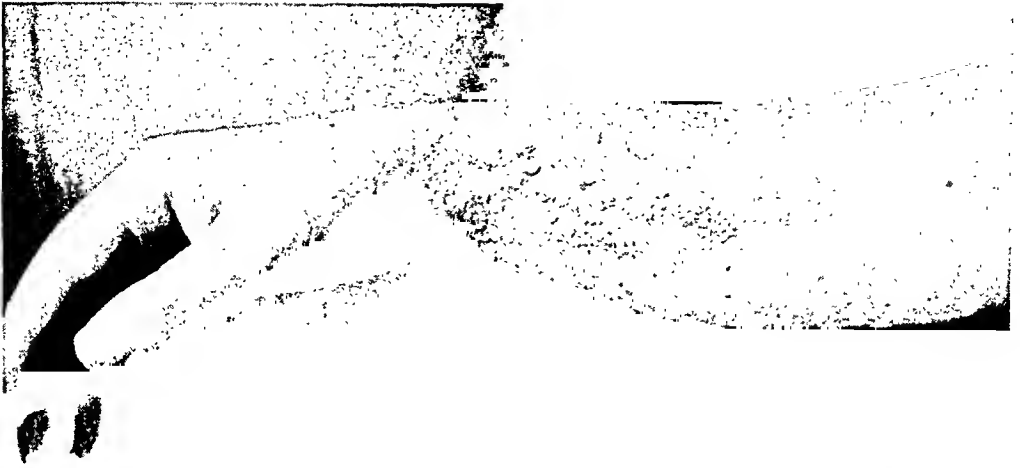


FIG. 10.—Case 5: Preoperative photograph of right forearm showing extensive adherent scar following healing of battle wound by secondary intention.



FIG. 11

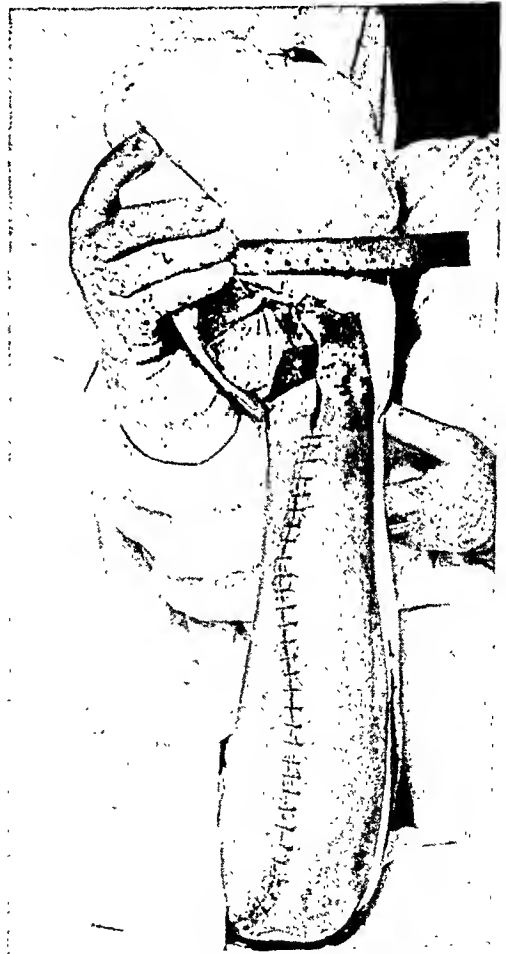


FIG. 12

FIG. 11.—Case 5: Postoperative photograph of volar surface, right forearm showing healed full-thickness graft.

FIG. 12.—Case 6: Operative photograph of the left hand and forearm showing skin defect due to excision of split-thickness graft and scar tissue. The neurorrhaphy has been completed.

ance is made for the distance between the abdomen and the base of the defect if they cannot be juxtaposed. The flap is raised to face either the flexor or extensor surface of the extremity according to the position of the defect, so that the abdominal wall is nearest its base. The full-thickness graft is raised at the level of the deep fascia. All donor areas thus far have been closed primarily. Our largest graft measures 15 x 10 cm. To facilitate closure, an incision is made on either side of and in line with the base of the pedicle, and triangular flaps are raised and rotated toward each other. After transection of the pedicle, revision of the wound of the donor area leaves a rather neat T-shaped scar. Silk technic is used throughout.

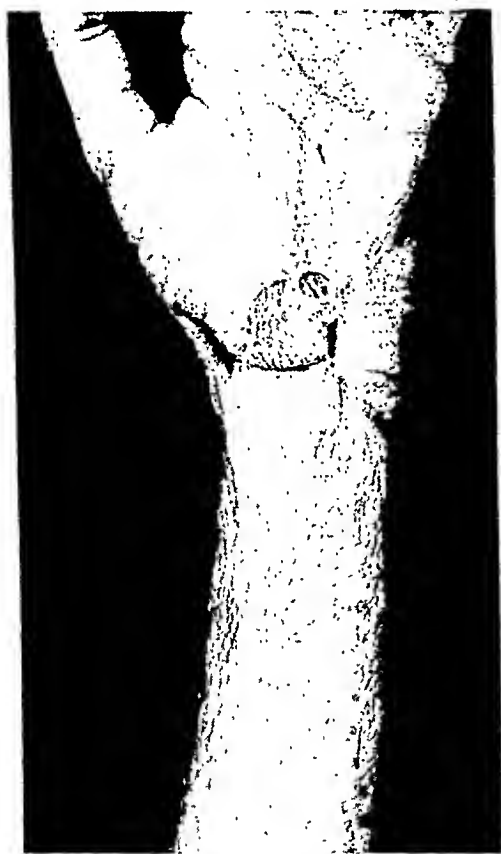


FIG. 13

FIG. 13.—Case 6: Postoperative photograph of left wrist showing healed full-thickness graft.



FIG. 14

FIG. 14.—Case 7: Preoperative photograph of right arm and elbow showing extensive deformity following loss of soft tissue.

It has been customary to transect the base of the pedicle in two, occasionally three stages. Transection has been completed in 15 to 21 days, depending on the width of the pedicle and the size of the graft as well as the circulatory appearance of the apex of the graft. A preliminary test by occlusion of the base with a rubber-covered intestinal clamp serves as a useful guide in determining the vascular independence of the graft. A proper amount of pressure is applied to the graft surface with a circular elastic bandage applied over mechanic's waste. Plaster of paris encasements have been used to secure immobilization until the graft has been freed from its source.

SUMMARY AND CONCLUSIONS

1. Peripheral nerve injuries complicating battle wounds of the extremities are often accompanied by soft tissue wounds which have been allowed either to heal secondarily or have been covered by split-thickness skin grafts.

2. Surgical defects resulting from removal of scar tissue of inadequate split-thickness grafts may be covered with full-thickness skin from pedicle grafts mobilized concomitantly with the neurosurgical procedure.

3. By combining these procedures definitive peripheral nerve surgery may often be completed earlier in the patient's convalescence.



FIG. 15.—Case 7: Preoperative photograph of lateral aspect of right arm and elbow showing extensive adherent scar overlying bone. The split-thickness graft has been used to secure early healing.

4. For defects of the upper extremity the abdominal or chest wall may serve as the donor site, for the lower extremity the surface of the opposite thigh may be used. The location of the donor site is often limited by the posturing necessitated by the neurosurgical procedure.

5. In most instances the defect created by raising the pedicle graft may be closed primarily by sliding flaps.

CASE REPORTS

Case 1

1. Date and type of injury:
3 August 1944. Flak injury.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
(a) Incomplete posterior tibial nerve paralysis, right.
(b) Avulsion of skin and soft tissues lower third of right leg.

PERIPHERAL NERVE INJURIES

3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) No nerve surgery.
 - (b) Wound healed by granulation in 6 months while a prisoner of war.
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 26 Nov. 1945—Neurolysis, posterior tibial nerve.
 - (b) 26 Nov. 1945—Pedicule flap from posteromedial aspect of left thigh.
 - 5 Dec. 1945—Partial section of pedicle, local anesthesia.
 - 11 Dec. 1945—Complete transection of pedicle, revision of donor site, spinal anesthesia.
5. Results of plastic procedures:

Graft healed without necrosis and without infection (Fig. 1).



FIG. 16

FIG. 16.—Case 7: Postoperative photograph corresponding to Figure 14. Note correction of soft tissue deformity.

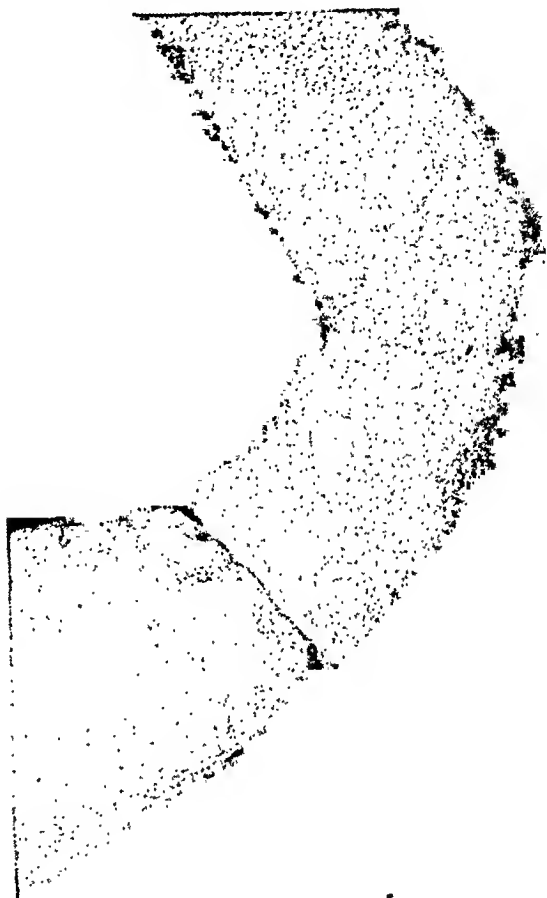


FIG. 17

FIG. 17.—Case 7: Postoperative photograph corresponding to Figure 15. Note removal of scar tissue.

Case 2

1. Date and type of injury:

7 January 1945. Mortar shell fragments.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
 - (a) Incomplete posterior tibial and superficial peroneal nerve paralysis, right.
 - (b) Avulsion of skin and soft tissues lower third of right leg with fracture, compound, comminuted, distal tibia.

3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) No nerve surgery.
 - (b) 5 Feb. 1945—Split-thickness graft to defect (Fig. 2).
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 6 Dec. 1945—Neurolysis—posterior tibial nerve.
 - 6 Dec. 1945—Pedicle flap from posteromedial aspect of left thigh.
 - 12 Dec. 1945—Partial section of pedicle, local anesthesia.
 - 21 Dec. 1945—Complete transection of pedicle, revision of donor site, continuous spinal anesthesia.
5. Results of plastic procedures:

Graft healed without necrosis and without infection (Fig. 3).

Case 3

1. Date and type of injury:

17 March 1945. Shell fragments.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
 - (a) Complete posterior tibial nerve paralysis, left.
 - (b) Loss of skin and soft tissues. Laceration of posterior tibial artery and vein.
3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) 18 March 1945—Approximation of nerve ends with black silk.
 - (b) 4 April 1945—Split-thickness graft to wound site.
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 27 Nov. 1945—Neurorrhaphy posterior tibial nerve, left.
 - (b) 27 Nov. 1945—Pedicle graft from posteromedial aspect, right thigh (Fig. 4).
 - 6 Dec. 1945—Partial section of pedicle, local anesthesia.
 - 12 Dec. 1945—Complete section of pedicle, revision of donor site, spinal anesthesia.
5. Results of plastic procedures:

Graft healed without necrosis and without infection (Fig. 5).

Case 4

1. Date and type of injury:

26 December 1944. Shell fragments.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
 - (a) Incomplete ulnar nerve paralysis, right.
 - (b) Massive skin and soft tissue loss with fracture, compound, comminuted, of distal end of humerus (Fig. 6).
3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) No nerve surgery.
 - (b) 19 January 1945—Split-thickness graft to right elbow.
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 12 Nov. 1945—Neurolysis and transplantation of right ulnar nerve.
 - 12 Nov. 1945—Pedicle graft from abdomen (Fig. 7).
 - 21 Nov. 1945—Partial section of pedicle, local anesthesia.
 - 29 Nov. 1945—Complete transection of pedicle, revision of donor site, inhalation anesthesia.
5. Results of plastic procedures:

Graft healed without infection but with a spotty area of superficial necrosis in its distal third. This healed fairly promptly without in any way endangering the purpose of the graft (Fig. 8). Donor site healed *per primam* (Fig. 9).

Case 5

1. Date and type of injury:

19 April 1945. Small arms fire.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
 - (a) Incomplete paralysis of median nerve, right.
 - (b) Skin and soft tissue loss with fracture, compound, comminuted, radius and ulna.

PERIPHERAL NERVE INJURIES

3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) No nerve surgery.
 - (b) Wounds healed by granulation following débridement (Fig. 10).
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 24 Oct. 1945—Neurolysis median nerve, right.
24 Oct. 1945—Pedicule flap from abdomen.
1 Nov. 1945—Partial section of pedicle, local anesthesia.
15 Nov. 1945—Complete transection of pedicle, revision of donor site, inhalation anesthesia.
5. Results of plastic procedures:

Graft healed without necrosis and without infection (Fig. 11).

4 Dec. 1945—Improvement in sensory and motor function permitting of neurosurgical clearance.

Case 6

1. Date and type of injury:

28 April 1945. Small arms fire.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
 - (a) Incomplete paralysis of ulnar nerve, left.
 - (b) Avulsion of skin and soft tissues.
3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) 23 Oct. 1945—Exploration of ulnar nerve. No suture performed.
 - (b) 5 May 1945—Secondary closure and split graft.
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 28 Nov. 1945—Neuorrhaphy and transplantation of left ulnar nerve (Fig. 12).
 - (b) 28 Nov. 1945—Pedicule flap from left costal margin.
7 Dec. 1945—Partial section of pedicle, local anesthesia.
13 Dec. 1945—Complete transection of pedicle, revision of donor site, local anesthesia.
5. Results of plastic procedures:

Graft healed after superficial necrosis of a small area (Fig. 13).

Case 7

1. Date and type of injury:

17 April 1945. Shell fragments.
2. Extent of injury to (a) nerve, (b) skin and soft tissue:
 - (a) Complete radial nerve paralysis, right.
 - (b) Avulsion of skin and soft tissues lateral aspect lower third of arm. Fracture, compound, comminuted, humerus with loss of bone substance (Fig. 14).
3. Previous operations (a) nerve, (b) skin and soft tissue:
 - (a) No nerve surgery.
 - (b) 14 June 1945—Split-thickness graft to skin and soft tissue defect (Fig. 15).
4. Reparative procedures (a) nerve, (b) skin and soft tissue defect:
 - (a) 23 Oct. 1945—Exploration of radial nerve. 8.5 cm. defect closed to 4 cm. by mobilization, patient is to have bone shortening at time of bone graft at a subsequent stage to permit of approximation of nerve.
 - (b) 23 Oct. 1945—Pedicule flap from abdominal wall.
31 Oct. 1945—Partial section of pedicle, local anesthesia.
7 Nov. 1945—Partial section of pedicle, local anesthesia.
14 Nov. 1945—Complete transection of pedicle. Revision of donor site. Inhalation anesthesia, ether.
5. Results of plastic procedures:

Graft healed without necrosis, but with minor wound infection along the proximal suture line. This readily subsided and patient is ready for combined nerve suture and bone shortening (Figs. 16 and 17).

THE USE OF RADIOACTIVE SODIUM IN THE STUDY OF PERIPHERAL VASCULAR DISEASE*

BEVERLY C. SMITH, M.D., AND EDITH H. QUIMBY, Sc.D.
NEW YORK, N. Y.

FROM THE DEPARTMENTS OF SURGERY AND RADIOLOGY, PRESBYTERIAN HOSPITAL, AND THE
COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK CITY, N. Y.

THE VIABILITY of an extremity depends upon blood delivered to it through the main and collateral arteries. Peripheral arterial disease affecting the walls of these vessels diminishes the local blood supply in different degrees with different types of pathology. It is very desirable in the treatment of peripheral vascular disease to have accurate information regarding the competency of the main and collateral arteries.

A procedure consisting of the introduction of radioactive sodium into the venous system, recording the time of its arrival at a part, usually the sole of the foot, and following the rate of accumulation of the material in that area, has been found useful in diagnosis, prognosis and evaluation of therapy in these cases. When this material is injected into a vein, it is rapidly mixed with the circulating blood. Since there is constant interchange of sodium between blood plasma and extravascular fluid, the amount of radioactive material in any region—*e.g.*, a foot—increases as it is brought there by the arterial circulation, passes through capillary walls and accumulates in extravascular fluid space. This increase continues until equilibrium is attained between intra- and extravascular sodium. The rate of increase and the final level attained depend upon the adequacy of the arterial circulation, the condition of the capillaries and the nature of the tissues. It has been found that the curve of the build-up to equilibrium can often be related to the degree of pathologic change in the vessels of the extremity.

Radioactive sodium (Na^{24}) is prepared in a cyclotron by bombarding sodium metaborate with deuterons. The metaborate containing the active atoms is dissolved in water, acidified with hydrochloric acid, and treated with methyl alcohol, resulting in the formation of methyl borate, sodium chloride and water. The solution is evaporated to dryness and heated, to destroy the pyrogens and to remove excess acid; the material is then dissolved in pyrogen-free distilled water, to give the desired concentration for injection, and autoclaved for one hour.¹ The radioactive atoms form a very small part of all the sodium in the solution, less than one in ten billion; the rest are the ordinary stable isotope. The two types of atoms are inseparable and indistinguishable until the radioactive ones disintegrate, emitting *beta* and *gamma* rays. A definite percentage of all the radioactive atoms disintegrate each second, and their disintegration can be detected by means of the Geiger-Müller counter.

In studies of peripheral vascular disease in the feet and legs, the patient lies on his back with his feet well-separated. The counter is placed against the sole of the foot (Fig. 1), and a measured amount of radioactive sodium, usually

* Aided by a grant from the Lilla Babbitt Hyde Foundation.

PERIPHERAL VASCULAR DISEASE

about 100 microcuries, in 3-7 cc. of sterile normal saline, is injected into an antecubital vein. Precautions are taken to see that all of the material gets into the vein and that neither the patient nor the injector is contaminated by it, if the latter is going to handle the counter. The times of the beginning and end of the injection are noted. Registration of the arrival of the radioactive material at the sole of the foot is made by an audible signal from a Geiger counter, with

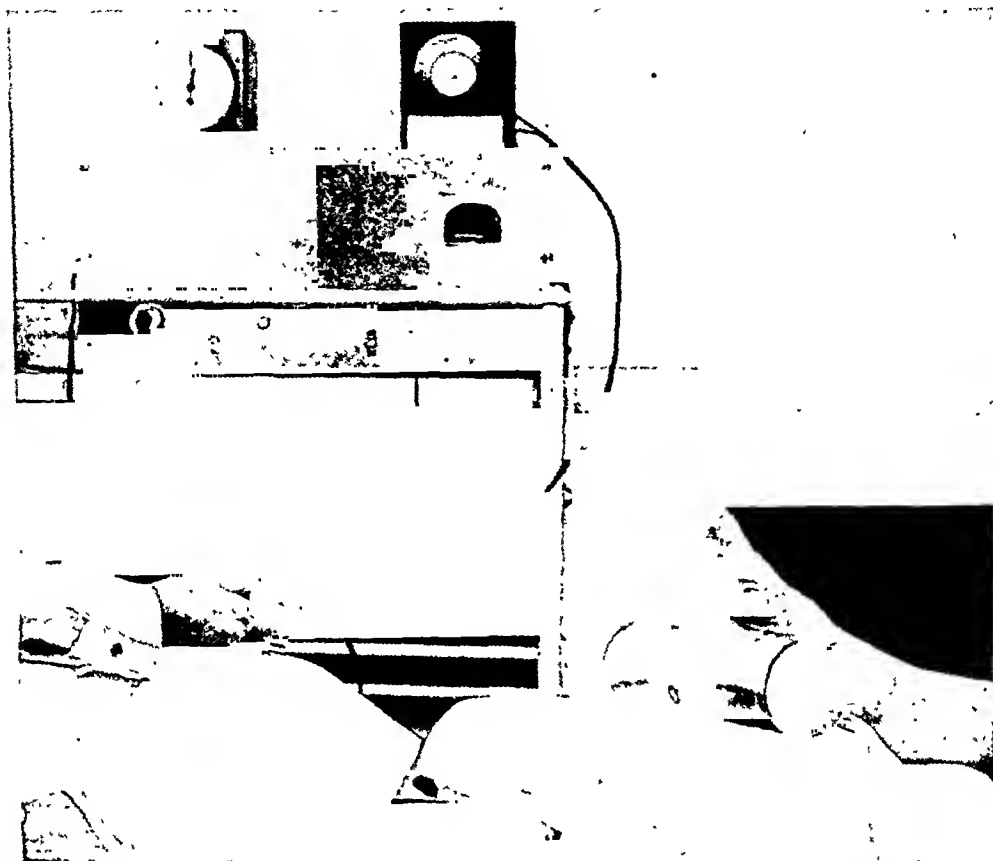


FIG. 1.—Geiger-Müller counting tube and scaling circuit. The shielded tube is shown in position against the foot of a patient.

an adjustable circuit so that the counting rate can be kept at a convenient level. Before injection there is a low background count due to cosmic rays and the presence in the vicinity of the apparatus of the radioactive material to be injected. When this material traverses the circulatory system and reaches the foot the counting rate increases sharply; in this manner the actual arm-to-foot circulation time can be measured. As the radioactive sodium leaves the capillaries and enters the extravascular fluid, build-up to equilibrium is manifested by the increase in counting rate. The "build-up curve" is plotted in counts per minute for 30-45 minutes, starting immediately after the injection.

Normals: This procedure has been carried out in 25 young normal individuals without clinical history or laboratory evidence of peripheral vascular disease; their curves all fall within the region indicated as normal range on the charts.

Charts of patients with peripheral vascular disease may fall below, within or above this range. Charts 1 to 6 record findings in various types of such

diseases, selected from some 300 patients who have been studied. In every instance the solid symbols represent counts at the sole of the right foot and the open symbols counts at the left foot.

ARTERIOSCLEROSIS

Each of these three patients had symptoms of several years duration. None had elevated blood pressure, and in none was the posterior tibial or dorsalis pedis artery palpable. All show curves somewhat below normal, except for the right foot of the case indicated by triangles (Chart 1).

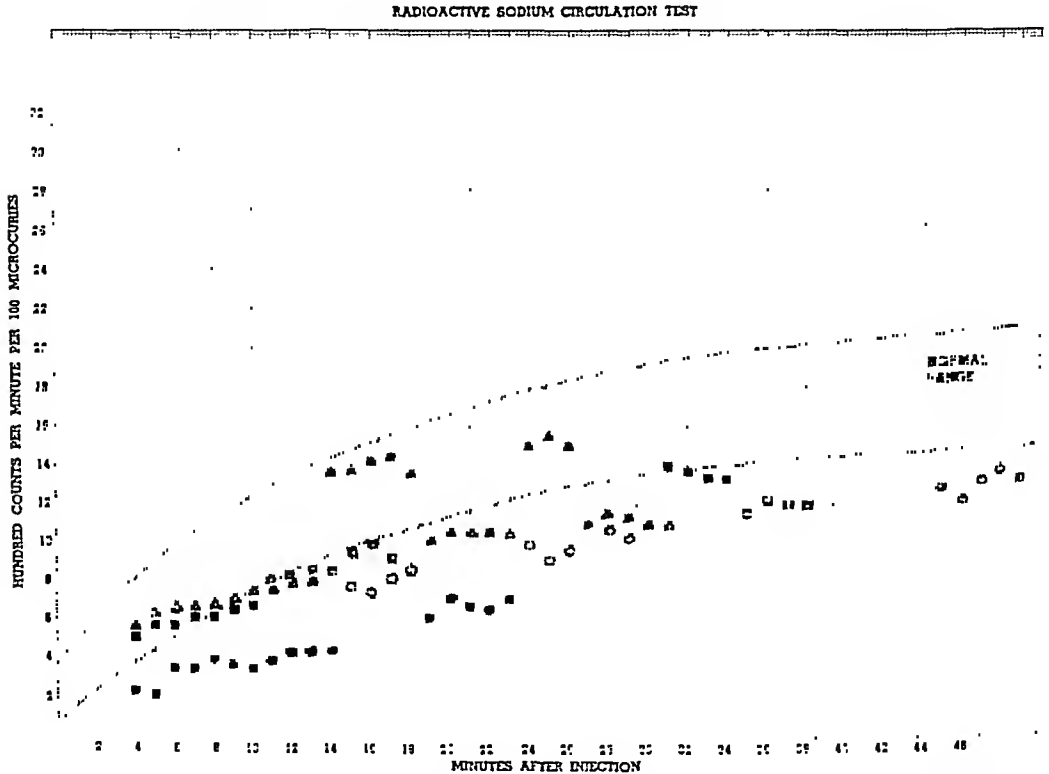


CHART 1.—*Arteriosclerosis*: For discussion of curves, see text. Closed symbols, counts against right foot; open symbols, counts against left foot.

Circles: Patient E. W.

Triangles: Patient B. C.

Squares: Patient A. S.

Circles: P. H. Unit No. 777381, E. W., a female, age 30, clinically improved on physiotherapy. The range of her reading in the absence of palpable main peripheral vessels indicates that her collateral circulation is reasonably well-established.

Triangles: P. H. Unit No. 722883, B. C., was a male, age 58, complaining of excruciating pain in both feet when they were dependent, and inability to walk. The left was worse than the right; he was incapacitated. Popliteal and femoral arteries were palpable: oscillometric readings extremely low. A modified guillotine amputation through the junction of the middle and lower third of the left leg was done, the stump healed by primary union. The arterial pathology of the specimen showed marked subintimal thickening in all arteries with occlusion and recanalization of the posterior tibial in the lower third of the leg. Three months later a similar amputation was performed through the right leg. The wound healed by primary union, and the pathology in the arterial

PERIPHERAL VASCULAR DISEASE

walls was identical with that of the left. The patient is using two artificial legs successfully. This patient's isotope curves are almost normal. The high readings on the right were due to mild inflammatory reaction. This degree of circulation was almost entirely the result of collateral, and was sufficient to permit primary healing following amputation. In the absence of pathology in the nerves of the amputated specimen, it appears that his exquisite pain was the result of local anoxia. This is the type of case in which the isotope curve indicated the probability of primary wound healing at the amputation site *below the knee*.

Squares: P. H. Unit No. 621627, A. S., was a male, age 40. This patient also had generalized xanthomatosis, with a serum cholesterol of 840 mg. per cent. No vessels were palpable in either extremity and oscillometric readings were very low. He has improved under physical therapy. Since the isotope study was made he has had a local thrombotic

RADIOACTIVE SODIUM CIRCULATION TEST

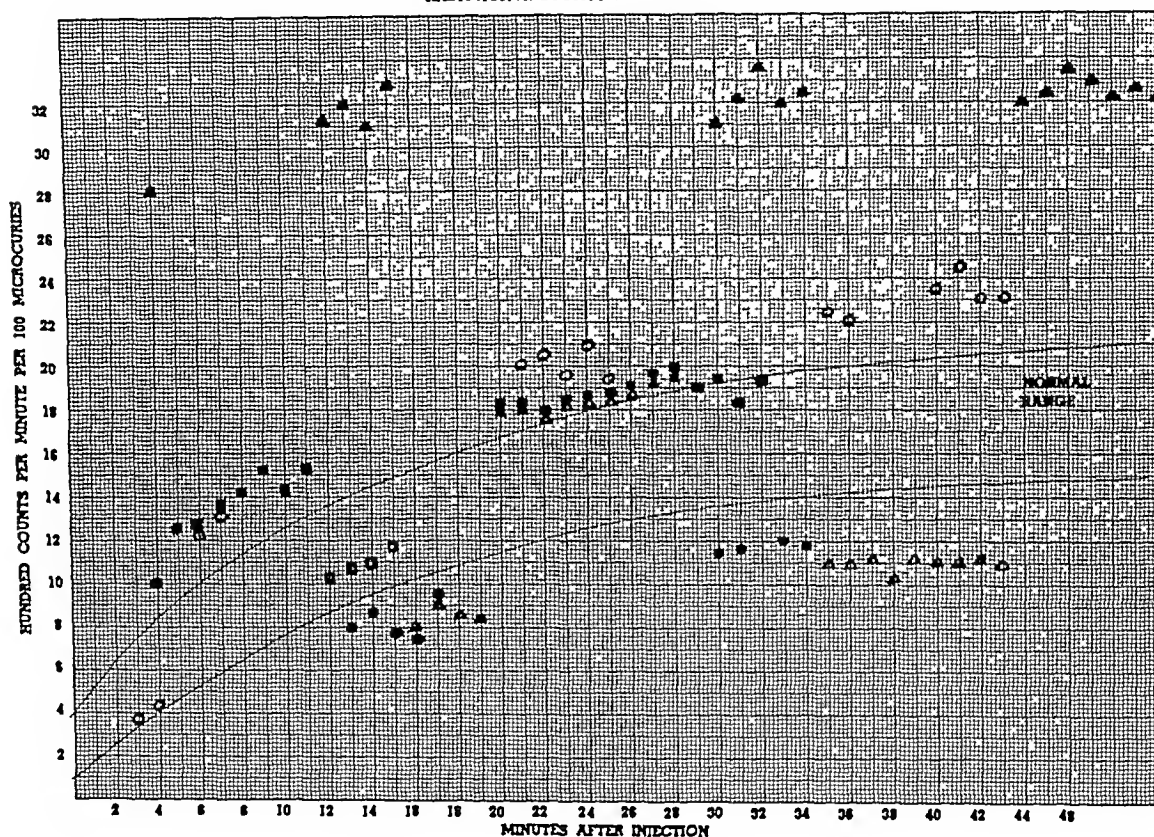


CHART 2.—*Diabetes with Infection*: For discussion of curves, see text. Closed symbols, counts against right foot; open symbols, counts against left foot.

Circles: Patient A. M.
Triangles: Patient E. G.
Squares: Patient A. P.

episode involving the dorsum of his right foot and three toes. He was treated conservatively, since his curve indicated adequate blood supply. In the absence of palpable main vessels, this was essentially all due to well-developed collateral circulation. On admission, he could not walk 100 feet; he can now walk slowly four miles.

DIABETES WITH INFECTION AND ARTERIOSCLEROSIS

These patients had moderate to severe diabetes of several years standing; all had serious infection in one foot. In all of them the counts at the infected foot were higher than normal, indicating good blood supply. Because of this, local surgery (amputation of toes) was carried out rather than amputation of the entire foot. Healing followed in all cases (Chart 2).

Circles: P. H. Unit No. 584036, A. M., was a female, age 61. Some time previous to the test she had had gangrene of the toes of the right foot, which had been amputated and healed. At the time of the study she had a cellulitis of the left second toe; the high readings indicated good blood supply, the toe was amputated and healed. Oscillometric readings were very low; there were no palpable arteries below the popliteal, the main digital vessels were thrombosed with calcification of their walls. The ample blood supply was due to well-developed collateral circulation.

Triangles: P. H. Unit No. 761577, E. G., was a female, age 63; osteomyelitis of right tarsus and fifth and third metatarsals, with swelling and cellulitis. Her main vessels were palpable. Material from a discharging sinus cultured a *Staphylococcus aureus* which was susceptible to penicillin. The very high radioactive sodium count indicated good blood supply and a favorable prognosis for conservative therapy. Sequestrectomy was done through small wounds, and an intensive course of penicillin established. The sinuses healed. The patient has been ambulatory for a year and a half with no complications.

Squares: P. H. Unit No. 639584, A. P., was a female, age 58; hepatosplenomegaly with diminished liver function, bilateral varicose veins and gangrene of the sole and toes

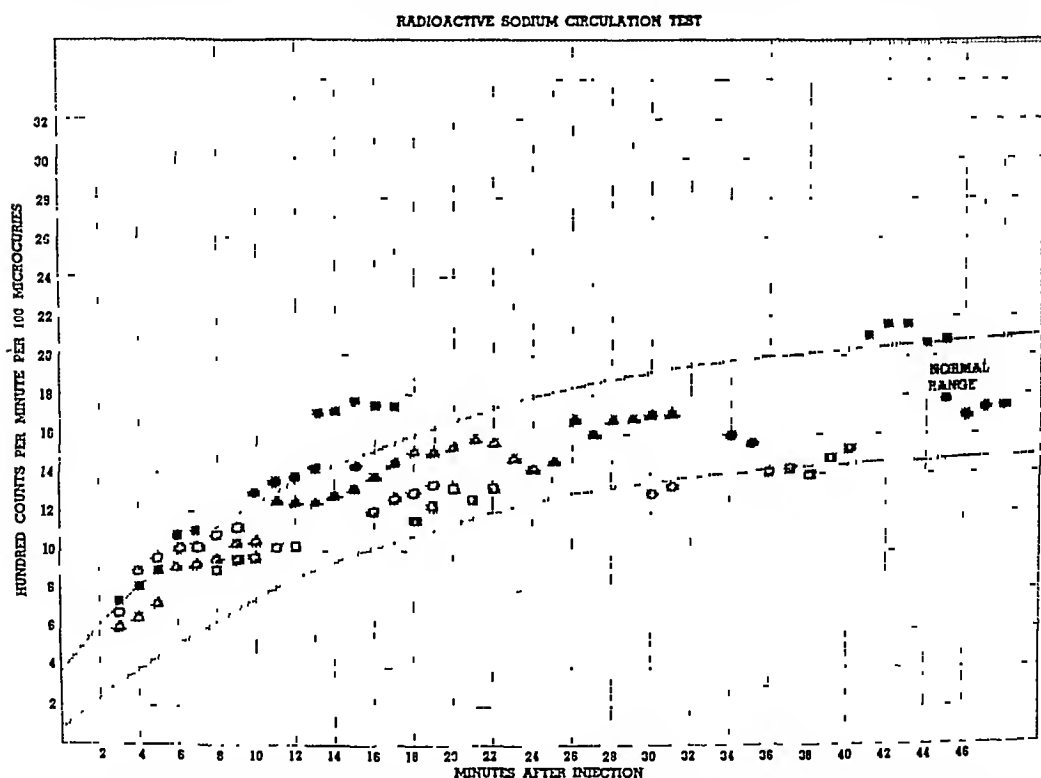


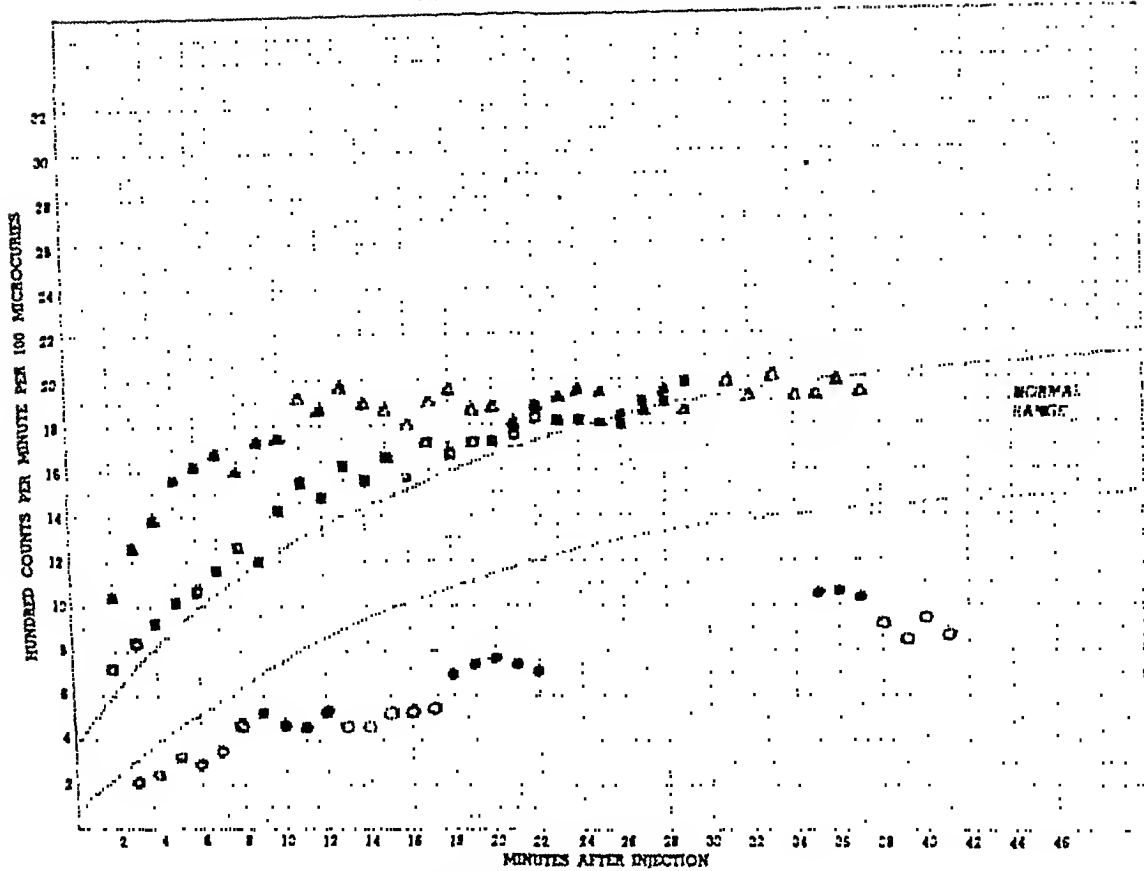
CHART 3.—*Thrombo-angiitis Obliterans*: For discussion of curves see text. Closed symbols, counts against right foot; open symbols, counts against left foot.

Circles: Patient R. S.
Triangles: Patient J. I.
Squares: Patient A. H.

of the left foot, following a burn from a hot water bottle; main vessels were palpable as far as the posterior tibial; the foot was completely anesthetic, due to diabetic neuropathy. An *hemolytic micro-aerophilic Streptococcus* and penicillin-sensitive *nonhemolytic* and *hemolytic Micrococci* were cultured from sloughing subcutaneous tissue. In view of the high count, local surgery was performed, the toes being amputated. (All surgery was performed without anesthesia.) An intensive course of penicillin was given. Healing was complete.

A

RADIOACTIVE SODIUM CIRCULATION TEST



B

RADIOACTIVE SODIUM CIRCULATION TEST

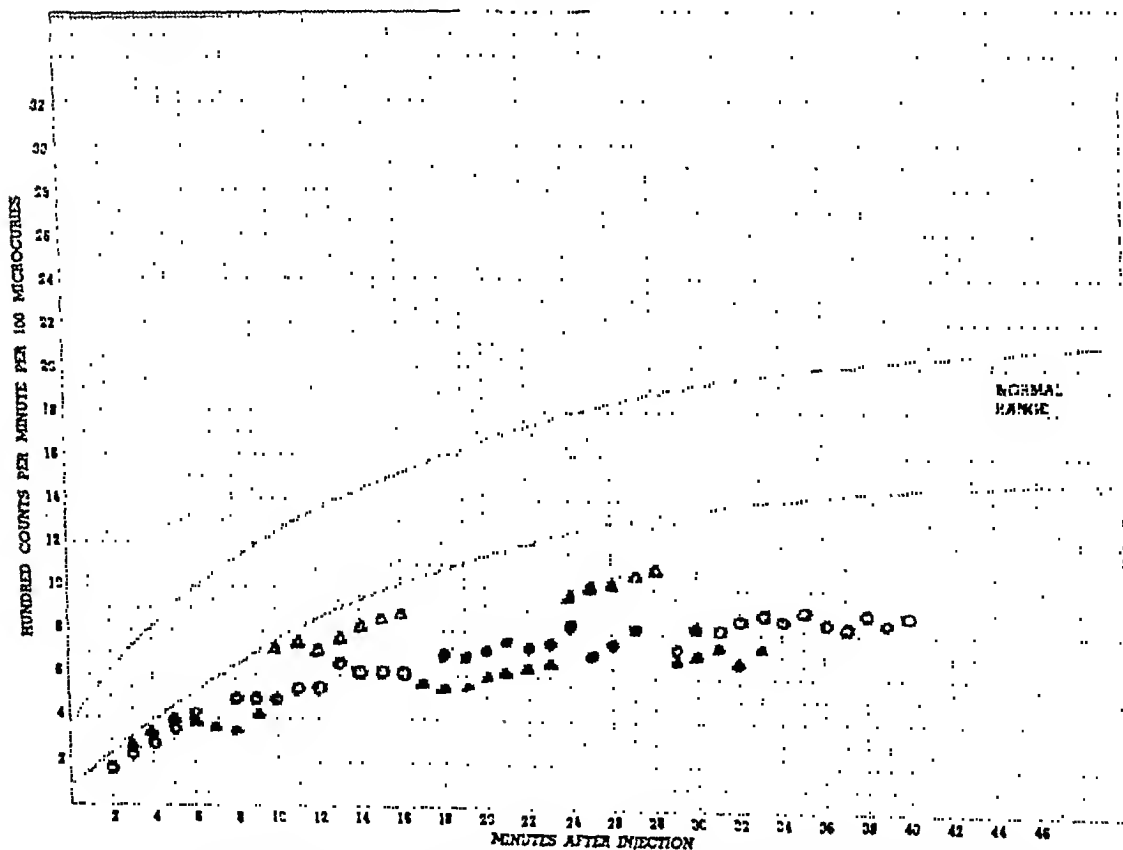


CHART 4.—*Hypertension*: For discussion of curves, see text. Closed symbols, counts against right foot; open symbols counts against left foot.

(A) Patient L. G.:

Circles: Before thoraco-lumbar sympathectomy.

Triangles: Three months after sympathectomy.

Squares: One year after sympathectomy.

(B) Patient A. S.:

Circles: Before sympathectomy.

Triangles: One year after sympathectomy.

THROMBO-ANGIITIS OBLITERANS

Two of these cases (one a woman) had active infection in one toe. The third had a spreading infection through his foot. All presented problems of treatment (Chart 3).

Circles: P. H. Unit No. 633731, R. S., was a female, age 30; gangrene of right great toe, associated with intermittent claudication of six months duration and multiple attacks of phlebitis. There was marked edema of the dorsum of the foot and exquisite pain. No arteries were palpable below the femoral, but the sodium curve in the high normal range indicated good collateral blood supply. Conservative surgery was done, consisting of amputation of the toe; healing occurred by secondary union, and there has been no further infection.

Triangles: P. H. Unit No. 44872, J. I., was a male, age 34. This patient had a history of six years duration; a peripheral novocaine crushing nerve block of posterior tibial, superficial peroneal and sural nerves of the left leg had been performed four years prior to the test; healing had been satisfactory. When studied, he had gangrene of the left great toe. With a sodium curve within the normal range, conservative surgery was expected to be successful; the toe was amputated and healed. There has been no further infection.

Squares: P. H. Unit No. 392546, A. H., was a male, age 38. Eight years before this study a novocaine and crushing nerve block had been done in the right leg, for relief of pain; an infected toe had healed. However at the time of the study the ulcer of the toe had recurred, and spread to the dorsum of the foot. The high count at the left foot indicated good blood supply but the spreading infection necessitated amputation of the leg at the junction of the lower and middle third. The wound is almost healed at present.

This is the type of case in which formerly amputation would have been performed above the knee because of uncertainty as to blood supply to allow for healing at a lower level.

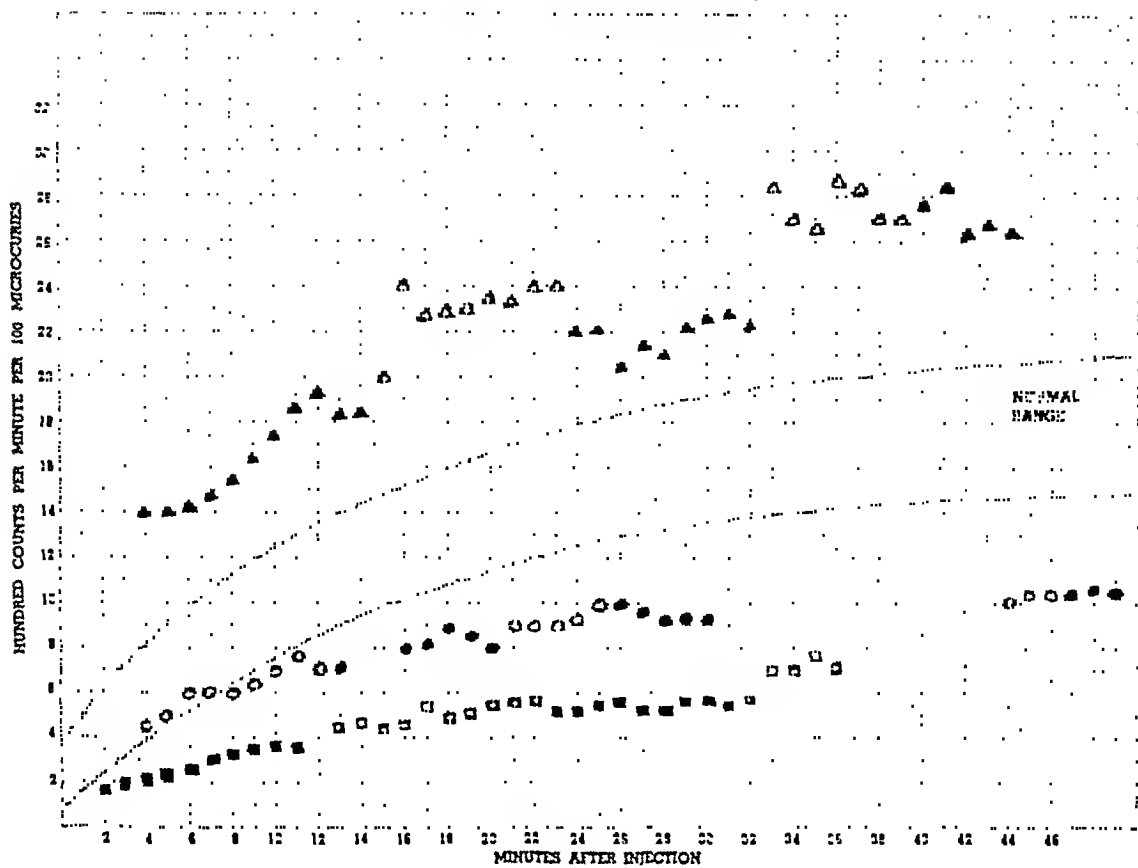
HYPERTENSION

The problem of hypertension deserves especial attention in connection with the radiosodium studies. Patients fall into three groups, with curves very low, somewhat low, and nearly normal. These respond differently to thoracolumbar sympathectomy. Those with very low counts before operation usually do well; they are relieved of symptoms, either with or without marked drop in blood pressure. The postoperative curve is well above normal. This indicates that the low first curve is due largely to peripheral spasm; when this is relieved vaso dilatation results. Most of the patients whose count is nearly normal before operation have either experienced severe vascular complication soon after operation or have died. Those in this group appear least likely to be benefited by this type of surgery. The middle group, those with moderately low initial counts, need further study; as they respond differently to surgery (Charts 4A and B).

Chart 4A: P. H. Unit No. 772853, L. G., was a male, age 40; B. P. 270/160; symptoms for two years; Grade 2 hypertensive retinopathy. He was bedridden, with headaches, dyspnea, and palpitation. The circles show his preoperative curve. Three months following thoracolumbar sympathectomy he returned to work symptomless; the triangles show his curve at that time. A year later he is still without symptoms, although his pressure remains high. The squares show his present curve.

A

RADIOACTIVE SODIUM CIRCULATION TEST



B

RADIOACTIVE SODIUM CIRCULATION TEST

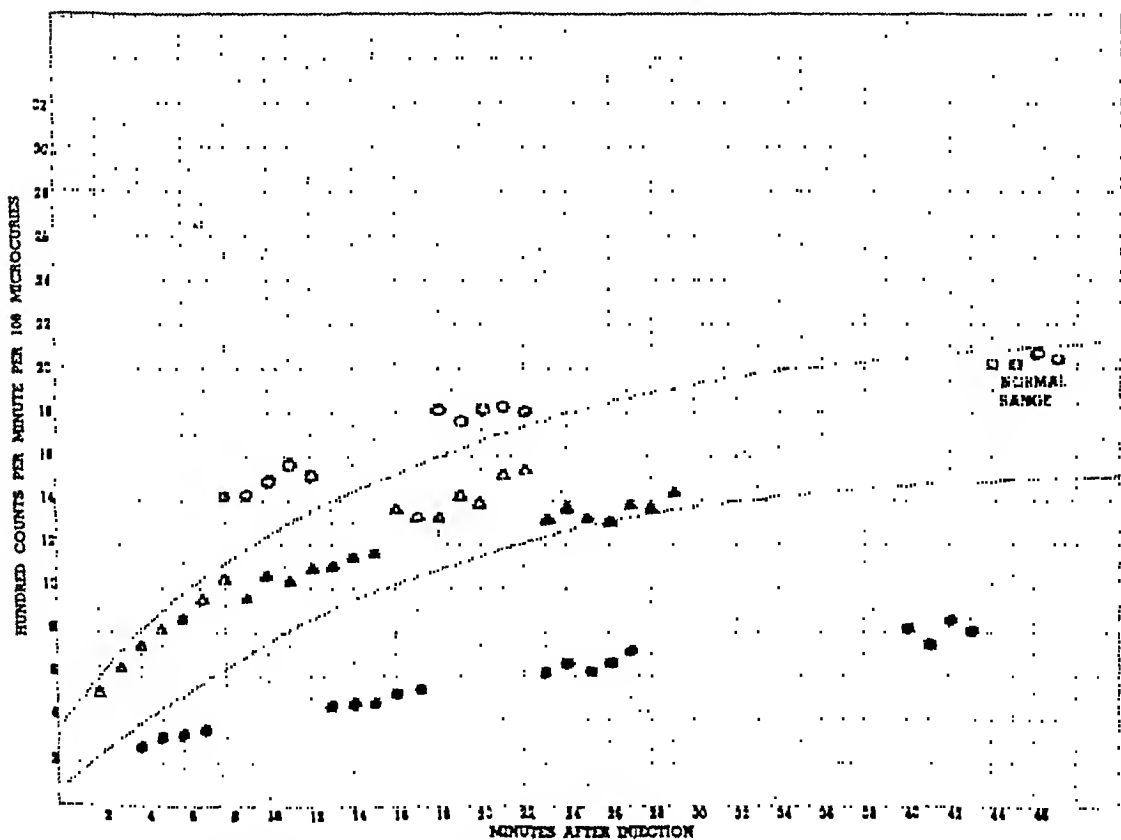


CHART 5.—*Immersion Foot and Frost-bite.* For discussion of curves, see text. Closed symbols, counts against right foot; open symbols, counts against left foot.

(A) Triangles: Patient E. M.: Frost-bite and infection.

Circles: Patient I. K.: Frost-bite without infection.

Squares: Patient J. W.: Immersion foot.

(B) Patient N. S.: Immersion foot.

Circles: One year after exposure; alcohol nerve block on left.

Triangles: Two and one-half years after exposure; alcohol nerve blocks on both sides.

Chart 4B: P. H. Unit No. 603879, A. S., was a female, age 40; B. P. 200/120; Grade 2 hypertensive retinopathy, advancing myocardial changes, no benefit from bed rest. The circles show her preoperative curve; the triangles show the situation two years later. She is asymptomatic; her pressure is 135/80. It was not possible to study her within the first year after the operation and there is no way of knowing whether she would have presented a high curve which returned to the lower range.

IMMERSION FOOT AND FROST-BITE

These patients usually have normally palpable arteries, but complain of pain on walking and of hypersusceptibility to cold. Their curves are low (Charts 5A and B).

Squares: No P. H. Unit No., J. W. (Chart 5A), 34-year-old seaman was examined in April, 1944, following a history of having been torpedoed in the northern Atlantic, February 23, 1943, and being in a life boat 17 days before rescue. During this time his hands and feet were frostbitten and he presented a typical picture of immersion feet from cold water. On examination, a year and one-half later, his extremities appeared perfectly normal; all of his arteries were normally palpable and his oscillometric readings were normal. He complained of pain only upon walking, in the soles of both feet, and of hypersusceptibility of both extremities to cold. His low curve indicates damage by cold with subsequent partial occlusion of the small arteries in the soles of both feet. This reading was the only objective laboratory finding in keeping with his clinical symptoms and upon the basis of it he was certified as not being fit for sea duty. There is no late follow-up on this case. Were it not for his low curve, this man would have been judged a malingerer.

Circles: P. H. Unit No. 419315, I. K., a 36-year-old male, froze his toes in 1934. This curve taken ten years later, indicates inadequate blood supply. The patient has had a coronary thrombosis, and probably now has peripheral arteriosclerosis, which may be worse because of the previous damage from freezing.

Triangles: P. H. Unit No. 777363, E. M., was a 39-year-old colored male. In 1940 his right foot was frostbitten and subsequently pain and ulceration developed in the great toe. This healed but reopened, and cultured a *nonhemolytic Streptococcus* and *Bacillus proteus*. The very high curve indicated patent main vessels, with inflammation, but it is not clear why the readings were also high in the uninvolved left foot. A partial amputation of the right great toe has been done, followed by a crushing nerve block because of persistent pain. The wound is still healing. The test will be repeated when healing is complete.

(Chart 5B), No P. H. Unit No., N. S., a 48-year-old Filipino steward, first seen in November, 1944, referred from the U. S. Marine Hospital for intolerance to cold and pain in feet, ankles, legs and knees. He had spent 19 days in an open life boat, subsequent to torpedoing of a ship in the South Indian Ocean in June, 1943. At the time of the examination, one year after exposure, the curve for the right foot was markedly low, while that in the left was above normal. He had had a left alcohol lumbar sympathetic block. These values are shown by the circles. The triangles give values obtained a year and one-half later, six months after a similar block had been performed on the right side. Both feet are now normal.

MISCELLANEOUS

Many cases which have been studied do not fall into well-defined disease groups. Nevertheless they warrant consideration as individual problems.

Circles: P. H. Unit No. 612902, A. D. (Chart 6A), was a white female, age 41. In 1940, she fell into a post-hole and her left leg became painful, blue, cold, and swollen.

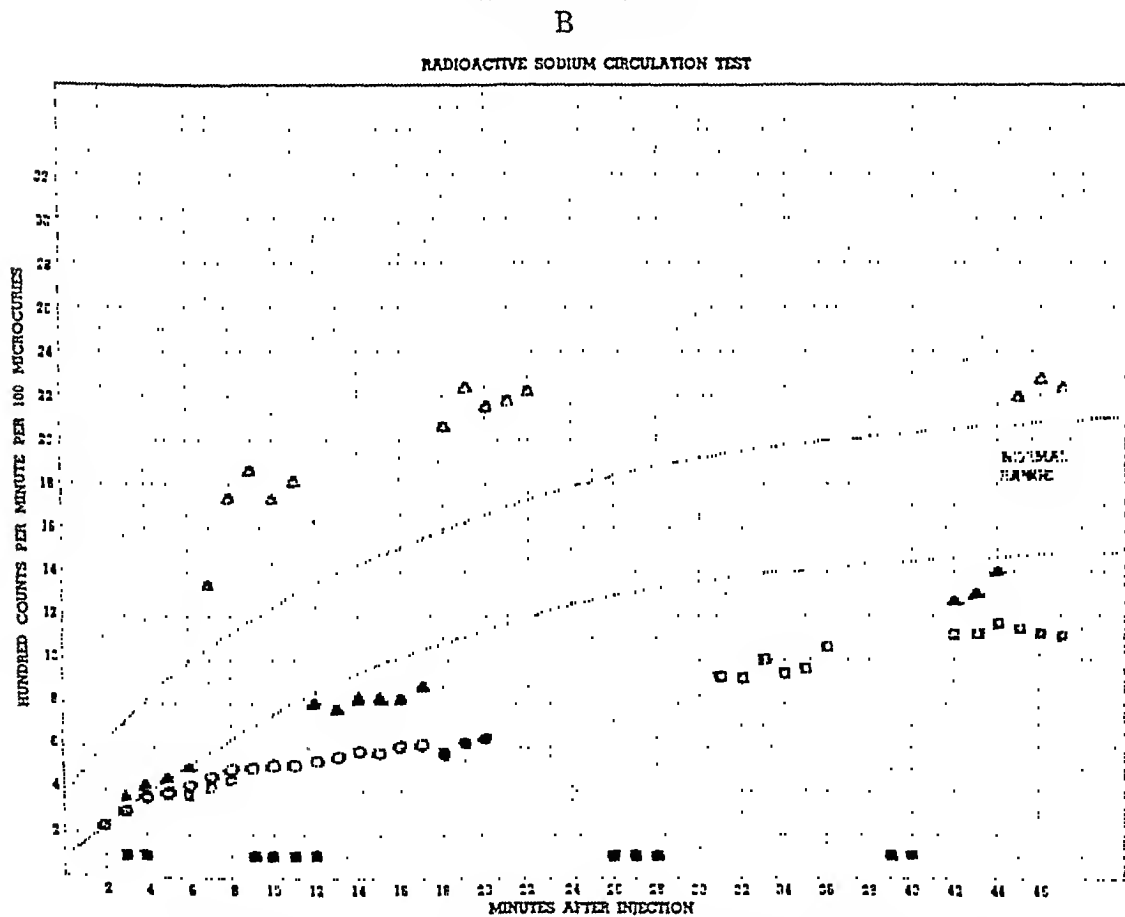
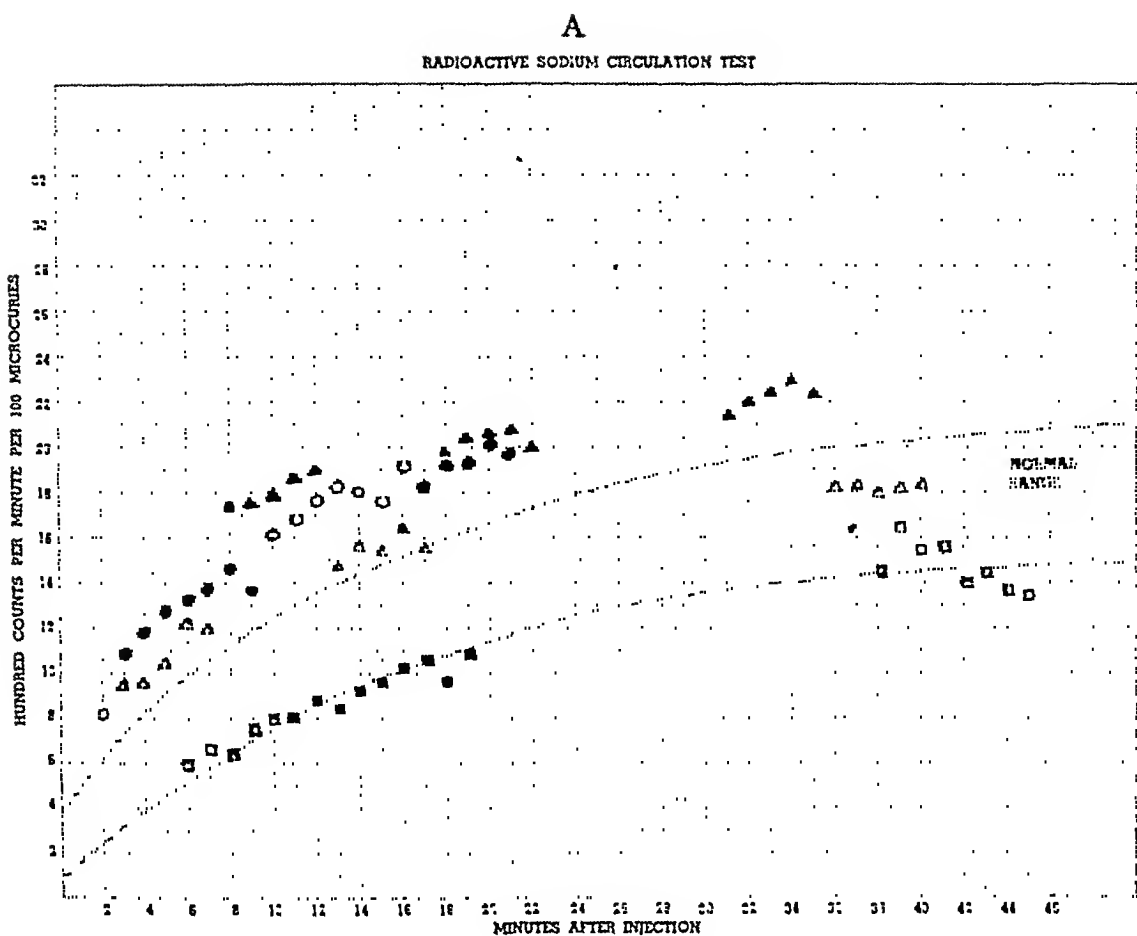


CHART 6.—*Miscellaneous*: For discussion of curves, see text. Closed symbols, counts against right foot; open symbols, counts against left foot.

(A) Circles: Patient A. D.: Accidental injury.
 Triangles: Patient J. R.: Cavernous hemangioma.
 Squares: Patient M. N.: Venous thrombosis.

(B) Triangles: Patient R. C.: Phlebitis.
 Circles: Patient I. M.: Scleroderma.
 Squares: Patient C. S.: Thrombosis of abdominal aorta.

Oscillometry was normal, roentgenograms negative, but function of the ankle joint was limited in all directions. Physiotherapy failed to relieve any symptoms. Following a left lumbar sympathetic novocaine block the temperature of this extremity rose 12° C. Accordingly, an excision of the left second and third lumbar sympathetic ganglia was done. The foot and leg became warm, all symptoms have disappeared, and the patient has returned to ambulatory occupation. It is to be regretted that a preoperative sodium study was not made. The postoperative curve is above normal for both feet. The high reading on the unoperated side suggests that some sympathetic fibers decussated and were destroyed by the operation on the left, thereby influencing the right.

Triangles: P. H. Unit No. 607824, J. R., was a Negro female, age 30, with a massive cavernous hemangioma of right inguinal region, buttock, thigh, and leg. The high reading on the affected side would be expected in view of large amount of extra blood in the leg.

Squares: P. H. Unit No. 555381, M. N., was a white female, age 33, with deep and superficial venous thrombosis of the right leg. The leg and thigh were so edematous that arteries could not be palpated. The normal sodium curve indicated that the block was not arterial, since the blood arrived there to deliver the material. Thrombophlebitic gangrene subsequently developed in both legs; the patient died. At autopsy, she was found to have carcinoma of the left intrahepatic bile duct, with carcinomatosis, and thrombi in many veins.

Triangles: P. H. Unit No. 803993, R. C. (Chart 6B), a male, age 38, sprained his right ankle, following which he developed phlebitis with pulmonary emboli. The femoral vein was ligated and found partly thrombosed. Sodium study at this time indicated adequate arterial blood supply in this leg. A modified guillotine amputation through the junction of the lower and middle thirds of the leg was performed, and the pathologic examination revealed a moderate degree of arteriosclerosis, with a calcification which had not severely compromised the lumen of any of the arteries. A generalized thrombosis and organization of all of the main arteries below the line of amputation had occurred. Some of the thrombi showed recanalization. Complete thrombosis of *all* deep and superficial veins in the leg and foot was present. At operation, not a single vessel was ligated. The wound healed by primary union, and the patient is wearing a prosthesis. The high sodium reading in the opposite extremity was probably due to inflammation there, which was clinically not detected until shortly after the study was made, when he developed phlebitis. The high count should have been a warning.

Circles: P. H. Unit No. 416356, I. M., was a male, age 29. Nine years before this study, a bilateral thoracolumbar sympathectomy had been done for Raynaud's syndrome. The benefit following this procedure was short-lived, the disease progressed to a typical generalized scleroderma, for which the patient was treated without success. The curve shows diminished blood supply. Death ensued six months later.

Squares: P. H. Unit No. 763262, C. S., was a male, age 44; thrombosis or embolus at bifurcation of abdominal aorta, with gangrene of both lower extremities, worse on the right. The extremely low reading at the right foot showed complete occlusion of all circulation, main and collateral, in this extremity. On the left, at the time of the test, some blood was being delivered. This later diminished, bilateral gangrene set in, and death ensued.

CONCLUSIONS

The use of radioactive isotopes as "tracers" has been found in many cases to supply a powerful new method for obtaining information of the status of the peripheral circulation. Radioactive sodium, introduced into a vein, is rapidly carried throughout all the blood vessels, and then passes through the capillary walls into the extravascular fluid. The arrival of the material at an extremity and the nature of its build-up there to equilibrium between intra-

and extravascular fluid can be followed with a Geiger-Müller counter. Curves plotted from these data give useful information regarding arterial blood supply to the extremity. By correlating this with clinical findings, conclusions can be reached regarding the degree of main or collateral circulation. In particular, estimates can be made of the degree of pathologic change in main or peripheral vascular disease.

Cases here presented indicate the manner in which the curves are used to determine when sufficient collateral circulation exists to warrant local conservative therapy. Similar studies at different levels of the leg have given valuable accurate information as to the site for amputation at which healing is to be expected. This has resulted in more amputations being done below the knee.

The group of essential hypertensives so far studied indicate a possibility that this test can be used to select cases which will or will not be expected to respond to thoracolumbar sympathectomy.

REFERENCE

- ¹ Smith, Beverly C., and Quimby, Edith H.: The Use of Radioactive Sodium as a Tracer in the Study of Peripheral Vascular Disease. *Radiology*, 45, No. 4, 335-346, October, 1945.

THE VALUE OF EXTERNAL SKELETAL FIXATION IN ELECTIVE ORTHOPEDIC SURGERY

CAPTAIN W. J. STARK, M.C.

VANCOUVER, B. C., CANADA

FROM THE SHAUGHNESSY HOSPITAL, VANCOUVER, B. C., CANADA

THERE have been many articles in the literature in recent years on the use of external skeletal fixation in the form of the Stader splint, the Haynes and the Roger Anderson apparatus for the treatment of fresh fractures. Scanty are the reports on the use of such devices in elective surgery on the skeletal system.

Roger Anderson pins and apparatus have been used at this hospital extensively in the treatment of fresh fractures, but the purpose of this communication is to outline its usefulness as a method of fixation in definitive operations upon the bones and joints.

The following is a study of 57 consecutive cases in which external skeletal fixation was used. All but one of these cases was operated upon by the author. The additional case was added to make the variety of cases included complete. The list includes bone grafting, arthrodeses, and shortening of the humerus to permit radial nerve suture (See Table I). The bone grafting operations have been carried out with full-thickness onlay or inlay grafts. Many cancellous bone grafts have been done as well with this method of fixation but they are not included in this paper and will be reported later.

OPERATIVE TECHNIC IN GENERAL

The appropriate size of pin is used for each bone or joint. For bone grafting, $\frac{5}{32}$ -inch pins are used for the tibia and femur, $\frac{4}{32}$ -inch pins for the humerus, $\frac{3}{32}$ -inch pins for the radius and ulna. For arthrodesis, $\frac{5}{32}$ -inch pins are used for the ankle and knee joint; $\frac{4}{32}$ -inch pins for the shoulder and elbow joint, and $\frac{3}{32}$ -inch pins for the wrist joint.

The pins are inserted by a slow speed hand drill which eliminates thermal damage to the soft tissues and bone.

The pins must be inserted at the exact anatomic site dictated. This is important to minimize pin complications. The insertion of the pins is done before the skin incision is made in nearly all cases.

In bone grafting, two pins are used above and two pins below the fracture site. These are usually half-pin units, but in the femur the lower pin is a through-and-through pin, and in the tibia the upper and lower pins are through-and-through pins. After the fracture site has been exposed and freshened and the position is corrected, the fracture site is fixed in a "known" position by locking the clamps of the Roger Anderson apparatus. The self-aligning splint may be used to secure the reduction of the fracture site, but this is not necessary. The application of the onlay graft is then very easy. If a sliding inlay graft is used in the tibia or femur the graft may be cut with no difficulty, using

EXTERNAL SKELETAL FIXATION

a motor saw if the pins are deliberately placed in the posterior cortex of the bone.

In arthrodesis, a different technic for each joint is used and will be described later.

Postoperatively, after the wound is healed, sterile gauze dressings securely wrapped around the pins are used. These are changed infrequently; since frequent dressings are unnecessary and there is danger of contaminating the pin sites. No plaster is used around the pins or around the extremity. The author does not believe this is useful.

Case Reports.—An example of each type of procedure listed in Table I is given. The majority of the cases had originally been compound fractures of the long bones in the shafts or involving the adjacent joints with or without previous osteomyelitis or septic arthritis. Most of the injuries were due to gunshot wounds. The indication for surgery in each case illustrated is fairly obvious from the roentgenographic appearance and a few words concerning the clinical condition preoperatively.

TABLE I
EXAMPLES OF EACH TYPE OF PROCEDURE

Procedure	Bone	No. of Cases	Average Period of Fixation
Bone Graft.....	Femur	10	20 weeks
	Tibia	15	18 weeks
	Humerus	8	14 weeks
	Radius	4	12 weeks
	Ulna	7	13 weeks
Shortening humerus		3	12 weeks
Arthrodesis (Joint):	Knee	4	14 weeks
	Ankle	2	16 weeks
	Shoulder	1	16 weeks
	Elbow	1	20 weeks
	Wrist	2	12 weeks
Total....		57	

COMPLICATIONS

(1) *Pin Seepage:* This occurred in 12 cases, or 21 per cent of the total cases. Shaar and Kreuz have stated that: "The most serious objection to external fixation is the possibility of infection from the use of pins. We have had no infections from pins in 157 consecutive cases. One must, however, differentiate between ordinary pin seepage and actual infection about the pin sites. A small amount of seepage occurs in about 10 per cent of cases." The author is certainly in full agreement with this statement. They list a number of causes of pin seepage but it is felt that movement of the skin and soft tissue about the pin sites is the cause of pin seepage in nearly every case in this series. Skin tension following insertion of pins, if it occurs, is dealt with by a counter incision in the skin in the operating theater. Pins are always inserted through normal tissue.



FIG. 1-A



FIG. 1-B

SUMMARIZED CASE REPORTS

Fig. 1A.—Case 1: Shows the roentgenographic appearance of a compound fracture of the right femur after eight months' immobilization in plaster. Clinically, there was motion at the fracture site and 35 degrees external rotation of the distal fragment on the proximal.

Fig. 1B.—Case 1: Anteroposterior view of the femur 14 weeks after a tibial onlay bone graft with Roger Anderson fixation. Early union is present. Immobilization discontinued 18 weeks postoperatively.

Fig. 1C.—Case 1: Photograph of the same patient with external skeletal fixation apparatus.



FIG. 1-C



FIG. 2-A

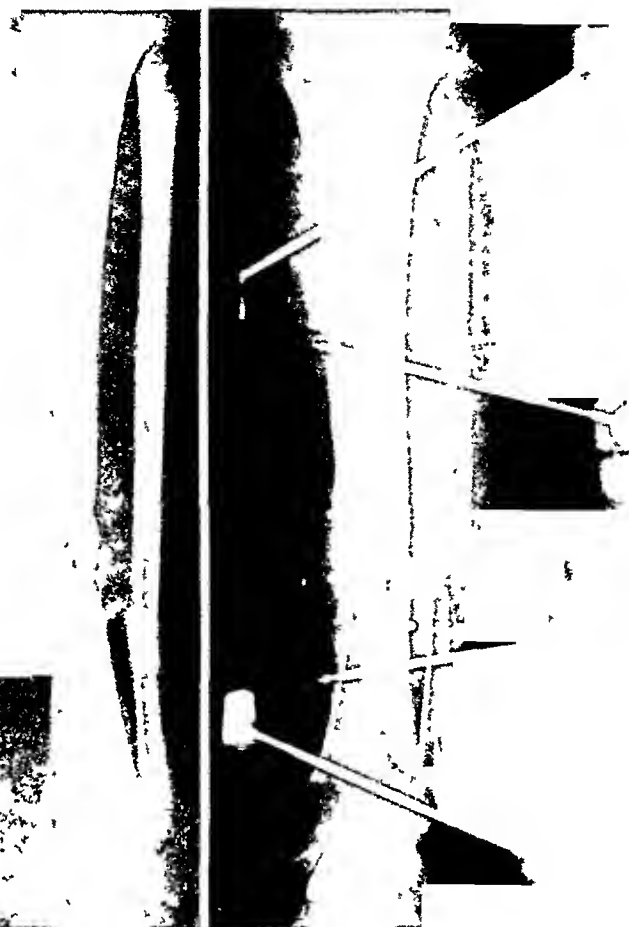


FIG. 2-B



FIG. 2-C

Fig 2A.—Case 2: Roentgenograms of a compound fracture of the tibia 10 months following gunshot wound. There had been continuous immobilization since this patient was wounded, including three months in a walking plaster. The skin wound had been healed for eight months.

Fig. 2B.—Case 2: Roentgenographic appearance 12 weeks after a sliding bone graft with additional cancellous bone from the opposite tibia. Immobilization discontinued in 16 weeks with union present.

Fig 2C.—Case 2: Photograph of the patient after surgery.



FIG. 3-A



FIG. 3-B

Fig 3A—Case 3: Roentgenographic appearance of an original compound fracture of the humerus on arrival at this hospital following seven months immobilization. His wound was well-healed

Fig. 3B.—Case 3: Fourteen weeks after a tibial onlay bone graft with additional tibial cancellous bone. Union is present.

Fig 3C—Photograph of a different patient who had also had a bone graft of the humerus with Roger Anderson fixation showing the position of the pins

Fig 3D.—Photograph showing range of abduction of the shoulder with external skeletal fixation apparatus six weeks postoperatively.

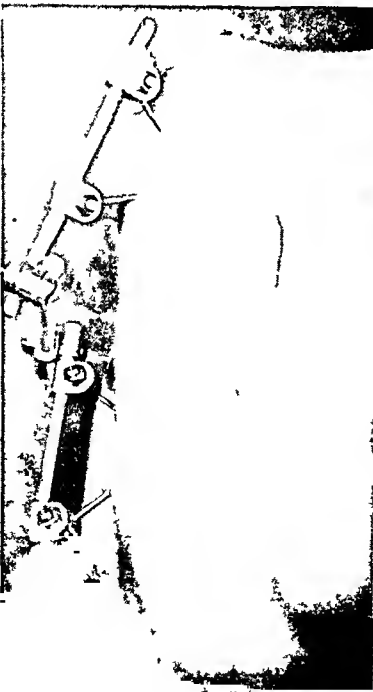


FIG. 3-C

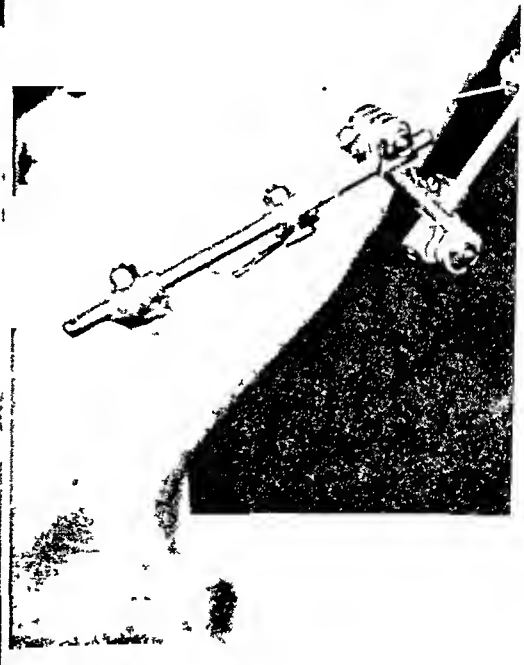


FIG. 3-D

EXTERNAL SKELETAL FIXATION



FIG. 4-A



FIG. 4-B

Fig. 4A.—Case 4: Roentgenogram showing preoperative appearance of a gunshot wound of the forearm and fracture of the radius. This patient also had a median nerve lesion which had been explored and sutured previously.

Fig. 4B.—Case 4: Roentgenograms six weeks following tibial onlay bone graft with cancellous bone. The upper pin is not in the elbow joint in the oblique roentgenogram. Union occurred in 12 weeks.



FIG. 5-A



FIG. 5-B

Fig. 5A.—Case 5: Roentgenographic appearance of a fracture of the ulna which was ununited clinically. The fracture was three years old and one previous bone graft elsewhere had failed.

Fig. 5B.—Case 5: Roentgenographic appearance 12 weeks after tibial onlay graft. Union is present. The lower pin is not in the radius in oblique views. Rotation of the forearm was possible during the healing period.

Fig. 5C.—Photograph of a different patient's forearm with fixation apparatus following bone graft of the ulna.

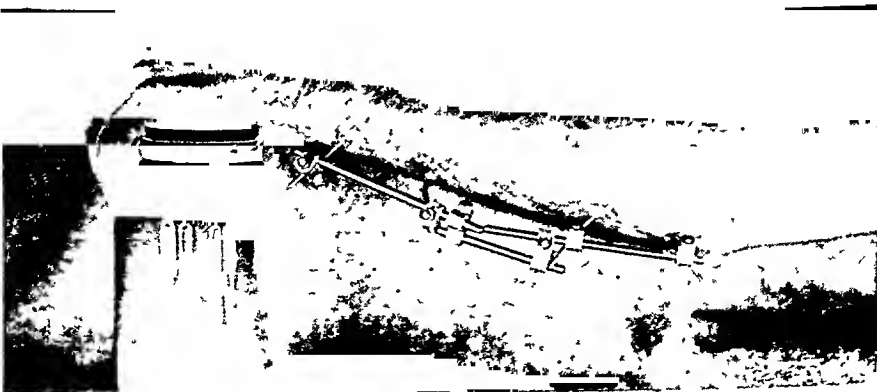


FIG. 5-C



FIG. 6

Fig. 6.—Case 6: Postoperative roentgenogram of a shortening of the humerus of 6.5 cm. to permit end-to-end radial nerve suture. An oblique osteotomy was used. The angulation at the osteotomy site was present before the Roger Anderson apparatus was locked. Pins remained in the humerus 12 weeks, when union occurred. Subsequently, there was recovery in the muscles supplied by the radial nerve.

Fig. 7A.—Case 7: Roentgenographic appearance of knee joint to months following a compound fracture of the tibia (gun-shot wound) involving the knee joint originally with osteomyelitis and septic arthritis.

Fig. 7B.—Case 7: Anteroposterior view of a surgical arthrodesis of the knee joint 10 weeks postoperatively. Early union is present. Immobilization discontinued in 14 weeks, when ankylosis was complete. Four $\frac{3}{32}$ -inch pins are used and their position is clearly indicated in the roentgenogram. The two oblique pins cross through the knee joint. The articular cartilage is removed from opposing joint surfaces before these oblique pins are inserted.



FIG. 7-A



FIG. 7-B



FIG. 8

Fig. 8.—Case 8: Postoperative roentgenogram of an arthrodesis of the ankle joint, with sliding tibial bone graft into the astragalus. This was a compound fracture of the lower tibia involving the ankle joint originally. Four $\frac{5}{32}$ -inch pins are used for fixation, two in the tibia and one each in the astragalus and calcaneus. The roentgenogram shows bony ankylosis of the ankle joint, which actually is fixed in 5 per cent of equinus.

Fig. 9A.—Case 9: Roentgenographic appearance of shoulder 18 months following gunshot wound. There was a neurotmesis of the circumflex nerve with complete deltoid muscle paralysis.

Fig. 9B.—Case 9: Appearance 10 weeks following arthrodesis of the shoulder joint with the use of a tibial bone peg driven through the upper humerus into the glenoid. External skeletal fixation. There are two $\frac{1}{2}$ -inch pins in the scapular spine, one through-and-through pin in the acromium and two half-pins in the humerus. Active motion in the elbow joint and scapulothoracic joints during pin fixation.

Fig. 9C.—Case 9: Roentgenographic appearance of the shoulder joint 16 weeks postoperatively showing solid bony ankylosis in 52 degrees of abduction. The humerus is in 30 degrees forward elevation at the shoulder joint.



FIG. 9-A



FIG. 9-B



FIG. 9-C



FIG. 10-A



FIG. 10-B

Fig. 10A—Case 10: Roentgenographic appearance of an arthrodesis of the elbow joint, with osteoperiosteal graft, two weeks postoperatively. Operation by Sqn Ldr. F. P. Patterson, R. C. A. F. The position of the $\frac{1}{2}$ pins are clearly shown in the humerus and ulna.

Fig. 10B.—Case 10: Roentgenographic appearance of elbow joint 20 weeks postoperatively. Solid bony ankylosis is present.



FIG. 11

Fig. 11.—Case 11: Roentgenographic appearance of an arthrodesis of the wrist joint using an osteoperiosteal graft 12 weeks postoperatively. The indication for surgery was a posttraumatic arthritis of the radio-carpal joint following old ununited fracture of the carpal scaphoid. The position of the $\frac{3}{32}$ -pins are shown in the roentgenogram; three half-pins in the radius, one half-pin unit in the second metacarpal shaft and one half-pin unit in the fifth metacarpal shaft. Radial-ulnar movement is preserved during the healing period. Bony ankylosis is present.

Pin seepage has never been serious and if local discomfort results, it is readily relieved by hot foment to the area for 24 to 48 hours. It most often occurred around the upper pin in the femur and humerus where the pin must penetrate a thick layer of muscle. To combat the problem in these locations it is helpful to insert the fixation pin slightly distal to the conventional position.

(2) *Pin Tract Infection:* This did not occur. In only three of the cases the pin sites did not heal in seven to ten days. All these three were completely healed in 15 days.

(3) *Osteomyelitis following Bone Penetration by Pins:* This did not occur.

(4) *Pin Sequestra:* None. Pins are inserted with a slow speed hand drill and this eliminates the element of thermal necrosis of bone.

(5) *Delayed Union and Nonunion following Bone Grafting:* There were no cases of nonunion. There were two cases of delayed union. One tibia required seven months to unite with continuous immobilization. This had been originally a compound fracture due to gunshot wound, with very poor bone substance at the fracture site as visualized at operation.

One femur in a mental case (schizophrenia) is not united nine months after operation. He had a severe wound infection postoperatively, with osteomyelitis. The infection is clearing at present and the graft is still bridging the fracture site. It appears that union will occur with further immobilization. It is to be noted that the infection at no time involved the pin tracts or the area of the femur which they penetrated. It was an infection of the operative site.

(6) *Exacerbation of Infection from Old Compound Wound:* This occurred

in four cases, without serious results. The operative incision was not affected. Bony union was not unduly delayed by this complication. In the four cases mentioned, the old wounds healed again in periods varying from three to eight weeks. This is not a high percentage when one considers the fact that in the series of 57 cases, 48, or 84.2 per cent, were originally compound fractures. Furthermore, elective surgery on bones and joints is being undertaken much earlier than the six to twelve months previously recommended, on cases which had originally been compound fractures due to gunshot wounds and were actually or potentially infected.

(7) *Postoperative Infection of Wound*: This was a case of a bone graft of the femur in a mental case which was discussed under "Delayed Union."

(8) *Renal Lithiasis*: No cases. Fractures of the femur and tibia and arthrodeses of the knee are ambulatory early.

SUMMARY

The advantages of external skeletal fixation when used in conjunction with bone grafting and arthrodeses are similar to those when this type of reduction and fixation is used in fresh fractures. We feel that Roger Anderson pins and apparatus are superior to other forms of external skeletal fixation for this purpose.

ADVANTAGES

(1) *Rigid and Continuous Fixation of the Fracture Site*: Plaster of paris encasements become loose and must be changed at intervals.

(2) *The Operative Procedure is Simplified*: Fixing the graft to the "host" bone is easier when the fracture site is held in a "fixed" position. Less fixation of the graft is necessary although this cannot be entirely dispensed with. Insertion of pins is much less exertion than applying a plaster encasement following the operation.

(3) *The Joints above and below the Fracture Site can be Mobilized*: This is done by physiotherapy to these joints during the healing process if they have been immobilized in plaster previous to surgery. Active motion of these joints is carried out postoperatively in all cases.

(4) *Early Ambulation is Provided* in the lower extremities except when a normal tibia is used to provide the graft for the injured tibia. Weight-bearing, with pins *in situ*, is allowed, commencing from eight to ten weeks postoperatively following operations on the lower extremities.

(5) *Minimal Nursing Care* is necessary for these patients.

(6) *Patients are Reasonably Comfortable*: In a survey of 20 patients who had been immobilized in plaster prior to surgery, 19 preferred the external skeletal fixation.

DISADVANTAGES

The disadvantages, of course, are the dangers of complications. These complications have been discussed. Although pin seepage was present in 21 per cent of these cases it was not a distressing feature and it can be minimized by precision in the placing of pins.

CONCLUSIONS

- (1) Roger Anderson pins and apparatus have proved useful in providing fixation in conjunction with bone grafting and arthrodeses.
- (2) The operative technic is discussed, and cases are briefly reported, with roentgenographic reproductions.
- (3) The advantages and disadvantages of the use of external skeletal fixation in this type of surgery are outlined.

The advice and encouragement of Dr. Jack Naden, civilian consultant to this Orthopedic Unit, is gratefully acknowledged.

REFERENCES

- Anderson, Roger: Fractures of the Radius and Ulna. A New Anatomical Method of Treatment. *J. Bone and Joint Surg.*, 16, 379, 1934.
- Idem*: An Automatic Method of Treatment for Fractures of the Tibia and Fibula. *Surg., Gynec. and Obst.*, 58, 639, 1934.
- Idem*: An Ambulatory Method of Treating Fractures of the Shaft of the Femur. *Surg., Gynec. and Obst.*, 62, 865, 1936.
- Idem*: Fractures of the Humerus. *Surg., Gynec. and Obst.*, 64, 919, 1937.
- Idem*: Ambulatory Method of Treating Femoral Shaft Fractures, Utilizing Fracture Table for Reduction. *Am. J. Surg.*, 39, 538, 1938.
- Idem*: Concentric Arthrodesis of the Ankle Joint: A Transmalleolar Approach. *J. Bone and Joint Surg.*, 27, 37, 1945.
- Anderson, R., and Burgess, E.: Delayed Union and Nonunion. *J. Bone and Joint Surg.*, 25, 427, 1943.
- Anderson, R., and Finlayson, B. L.: Sequelae of Transfixation of Bone. *Surgery*, 13, 46, 1943.
- Anderson, R., McKibbin, W. B., and Burgess, E.: Intertrochanteric Fractures, Nonoperative, Castless, and Ambulatory Method of Treatment. *J. Bone and Joint Surg.*, 25, 153, 1943.
- Bradford, C., and Wilson, P. D.: Mechanical Skeletal Fixation in War Surgery. *Surg., Gynec. and Obst.*, 75, 468, 1942.
- Haynes, H. H.: Skeletal Fixation of Fractures. *Am. J. Surg.*, 59, 25, 1943.
- Johnson, R. W., and Lyford, J.: The Use of the Haynes Skeletal Fixation Apparatus in Definitive Orthopedic Surgery. *J. Bone and Joint Surg.*, 26, 475, 1944.
- Junkin, H. D.: The Topography of Pins: Precision Pinning of Fractures. *Industrial Medicine*, May, 1944.
- Lewis, K. M., Breidenbach, L., and Stader, O.: The Stader Reduction. Splint for Treating Fractures of the Shafts of the Long Bones. *Am. Surg.*, 116, 623, 1942.
- Mazet, R.: The Use and Abuse of the Anatomic Splint in the Treatment of Fractures of the Lower Extremity. *J. Bone and Joint Surg.*, 25, 839, 1942.
- Shaar, C. M., and Kreuz, F. P.: Manual of Fractures. Treatment by External Skeletal Fixation. Philadelphia, W. B. Saunders Co., 1943.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

Walter Estell Lee, M.D.

1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY

East Washington Square, Philadelphia, Pa.

ANNALS OF SURGERY

VOL. 125

APRIL, 1947

No. 4



COMPOUND INJURIES OF THE KNEE JOINT*

STUDY II—THE INFECTED KNEE JOINT

JOE M. PARKER, M.D., AND JOHN J. MODLIN, M.D.

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, SAINT LOUIS, MISSOURI

WORLD WAR II has witnessed a significant change in the surgical treatment of severely traumatized and infected knee joints. Because of the dreaded nature of this injury and its complications, the emphasis during the latter part of World War I and the early phases of World War II was placed largely on the saving of life and limb. With the advent of penicillin and the more certain control of infection, a more ambitious goal, the conservation of a functioning joint, has become a possibility. It is to record the feasibility of this constructive approach to the problem that this paper is presented. The conclusions are based on the series of cases seen at the 21st General Hospital during the African, Italian, and French campaigns.

Prior to the general use of penicillin, infection was regarded as inevitable in a considerable number of cases. Treatment was confined to the provision and maintenance of adequate drainage for as long as necessary. At present, the contention of the authors is that established infection can be controlled and a functioning joint obtained if the following conditions can be met: (1) Removal of all actually or potentially devitalized tissue and foreign material which can serve as foci of infection. (2) Control of the residual infection by the systemic and intra-articular use of penicillin. (3) Closure of the knee joint to exclude reinfection from without, and to insure retention of the penicillin. (4) Institution of early, active motion.

Not all infected knee joints can be salvaged, since it may be impossible adequately to débride and yet preserve the joint; or, the soft-tissue loss may be of such magnitude that it is impossible to close the joint. Thus, it becomes impracticable to attempt débridement for the extensively shattered joint which is infected. The infected joint most amenable to the therapy outlined is the one with minimal fracture.

During the African campaign, when the traditional concepts of care of

* From the 21st General Hospital (Washington Univ. Unit).

suppurating arthritis of the knee joint were followed, excellent results were achieved, if judged solely by the fact that there was no death at our hospital attributable to this condition. Furthermore, in no instance was joint suppuration an indication for amputation. However, these results were achieved at the price of a prolonged convalescence and usually a permanent loss of function of the knee joint. The method employed was exteriorization or drainage of the joint by medial and lateral parapatella incisions and prolonged immobilization. While the more fulminating and acute manifestations could thus be controlled, it gradually became apparent that they were followed by a low grade, smouldering infection that eventually led to the development of a stiff joint.

The change of approach in the care of infected knee joints occurred in Italy in the early Spring of 1944. At this time penicillin became generally available, and the concepts of early reparative surgery were developed. These principles, as outlined by Col. E. D. Churchill, were tirelessly disseminated by Major Champ Lyons and Lt. Col. Oscar P. Hampton, Jr., who taught the physiologic and surgical principles that must be observed in the proper use of penicillin and foresaw the possibilities of exploring and closing the infected joints in order to spare the patients the effects of continued suppuration.

During this period, the hospital functioned in the Base, receiving patients directly from Evacuation Hospitals within two to eight days of wounding. It served in a similar capacity later, in France, although evacuation there was not always as prompt. A total of 244 penetrating and perforating wounds of the knee joint were treated. Of these, 29 developed clinical infections of the knee joint.

Clinical Manifestations of Infected Knees.—The campaigns in Italy and France have provided a very unusual opportunity for study of the problem of suppurative arthritis of the knee, as 29 cases have been seen, and 15 of these have been subjected to operation. These experiences have led to the conclusion that, in general, three stages or degrees of suppuration may be seen in knee joints: acute, subacute, and chronic. Unless the process is arrested, however, all lead to the same end—destruction of the joint surfaces. Of these stages, the last, the chronic joint suppuration, is by far the most subtle, and is most likely to escape diagnosis.

(1) Acute suppuration of the knee joint is not a common complication of war wounds. There have been instances, however, from penetrating wounds. The clinical picture is that of marked systemic reaction, with high fever, leukocytosis, prostration, and excruciating pain on motion of the knee. The knee is red, swollen, and very tender. A joint with fulminating infection is usually greatly distended. The wound may show the escape of seropurulent or purulent fluid, the amount depending on the ease with which the fluid has been escaping from the joint through the wound.

(2) The subacute, suppurating joint is the one most frequently seen. The symptoms are not so severe as in the acute type. Fever may be recorded between 102°F. and 103°F. The pulse rate is slightly accelerated. The knee is swollen and tender. Redness and tenderness are not so marked as in the

COMPOUND INJURIES OF KNEE JOINT

acute, fulminating joint. There is pain on motion, a very important sign. If left without treatment, the subacute joint may develop into the acute, fulminating pyarthrosis. Case history No. 1, under "Supplement," is submitted to illustrate the points of definition of the subacute suppurating joint.

(3) The chronic suppurating joint is likely to escape diagnosis because the symptoms are low-grade. Prolonged daily fever of perhaps only 99°F . to 99.6°F . is recorded, and there usually persists a slight acceleration of the pulse. The knee joint is tender and motion causes pain, again, a most valuable sign. The wound itself fails to heal and there is an escape of purulent material from sinuses leading to the joint. Unless watched for, this drainage may be so small in amount that it may go undetected. The chronically infected knee may be

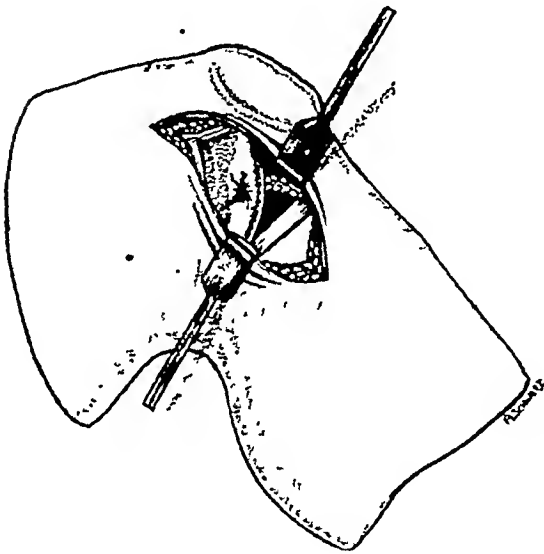


FIG. 1-A

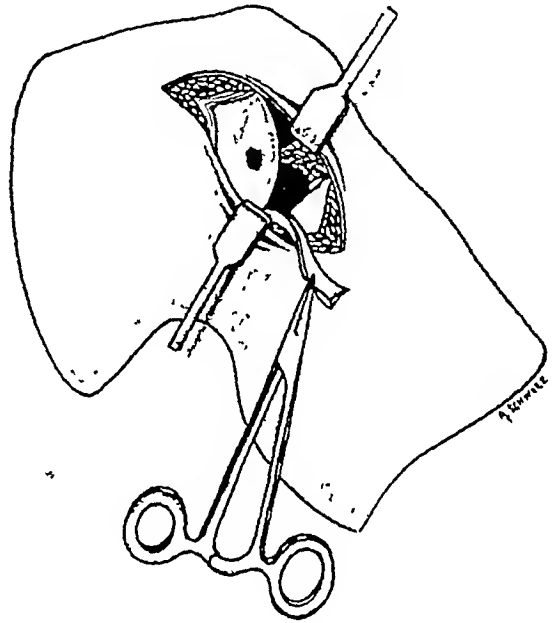


FIG. 1-B

FIG. 1.—(A) Septic knee joint with extension of previously débrided wound to permit adequate visualization of interior of joint. Note penetrating wound of medial femoral condyle.

(B) Same joint after curettage and débridement of condylar defect and detachment of anterior portion of medial meniscus.

the result of persistence arising from inadequate treatment of the subacute joint. It is the type of reaction that develops when the joint is left open because soft-parts are insufficient to close-off the joint cavity. As the name implies, it is a late stage of a continuing suppuration.

In addition, most of these patients are anemic from continual blood destruction and require repeated transfusions. They exhibit weight loss and cachexia. If the problem is complicated by wounds of other systems or organs, the diagnosis may be difficult. A typical example of the chronic suppurating joint is submitted as Case No. 2 in the "Supplement."

Gross Pathology of the Different Stages.—(1) In the acute, septic joint, the periarticular structures are edematous and the synovium is thick and

injected. Fibrin accumulations with purulent degeneration within the joint are common. A careful search within the joint will usually reveal the devitalized area wherein the infection had its origin. In the early, acute, suppurating knee joint, the menisci appear viable, but because of their normal avascularity and lack of resistance to infection, it is impossible to be certain of their continued viability.

(2) In the subacute joint, which is usually seen and operated upon somewhat later, degeneration of the menisci may be evident. This is the type of suppurating joint in which it is common to see retained foreign bodies, with articular damage. When the meniscus is devitalized, it becomes dull, yellowish, and soft. Usually, the meniscus on the side of the wound is the first to undergo degeneration.

(3) The chronically suppurating joint is, as the name implies, an older process, with definite progressive destruction of its most susceptible structures. The menisci are generally found degenerated, and the areas of contact between the tibial and femoral condyles may be in various stages of erosion, with loss of the cartilaginous surfaces. The same process may be noted between the patella and the femoral condyles. The articular cartilage in contact with the devitalized meniscus may also be degenerated. These various degrees of destruction were described by Phemister in 1924. In the chronic stages, the hyperemia of the more fulminating process is lacking. There may be partial obliteration of the joint cavity by fibrous adhesions. The chronic stage is an indolent process associated with the gradual destruction of articular cartilage and later involvement of the underlying bone.

Treatment of the Infected Knee.—The primary assumption made by the authors in the treatment of infected joints is that the joint defends itself best as a completely closed cavity. The first goal, then, is to restore the joint as a closed space. Furthermore, penicillin can be kept in the greatest concentration within the joint if the latter is water-tight. Next, an attempt is made to eliminate all dead tissue within the joint. Thus, reliance is placed on the inherent ability of viable structures with adequate blood supply to resist the action of invasive bacteria, aided to some extent by penicillin.

Without doubt, good results have been obtained in the past by arthrotomy and drainage of the joint. It is possible, however, that it was the ability of the synovium to seal itself off rapidly that led to the favorable outcome, and that joints which did not cease draining shortly developed cartilaginous damage.

Actually, all the infected joints that were the result of relatively minor injuries, revealed undébrided, damaged cartilage or bone, and this was felt to be the origin of the infectious process. To quote an axiom of reparative surgery: "Penicillin will not sterilize devitalized tissue." The natural resistance of undamaged knees to withstand the trauma of exposure and exploration is impressive. It would seem that infection rarely develops in the knee that has no devitalized tissue to serve as the nidus for infection. The one exception to this is the joint constantly contaminated by an infected fracture site.

Once the infectious process is started, however, the various structures within the joint possess definite but different powers of resisting the necrotizing

COMPOUND INJURIES OF KNEE JOINT

effect of suppuration. In turn, these devitalized structures sustain and prolong the infection. Of all the structures within the joint, the menisci are the least able to resist this necrotizing action. After the menisci, the articular cartilage, especially where contact between condyles occurs, is most apt to necrose.

Based on these facts, the approach to treatment of suppurating knee joints has been directed toward excising the menisci, performing a thorough and meticulous excision of all detached, devitalized cartilage and bone, and removing all foreign bodies found within the joint. The joint is then closed, and

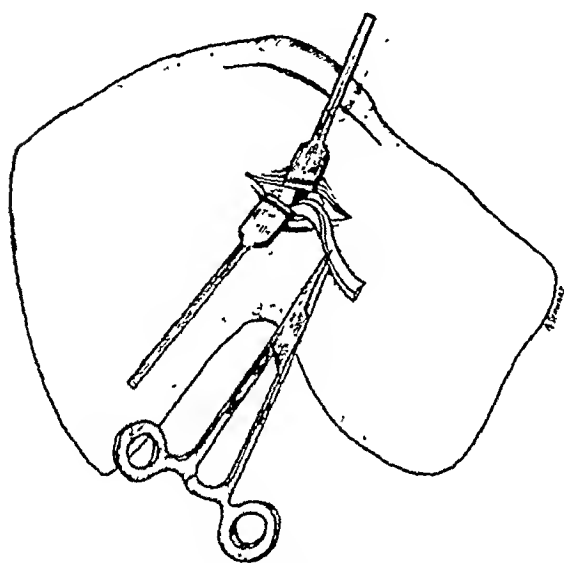


FIG. 2

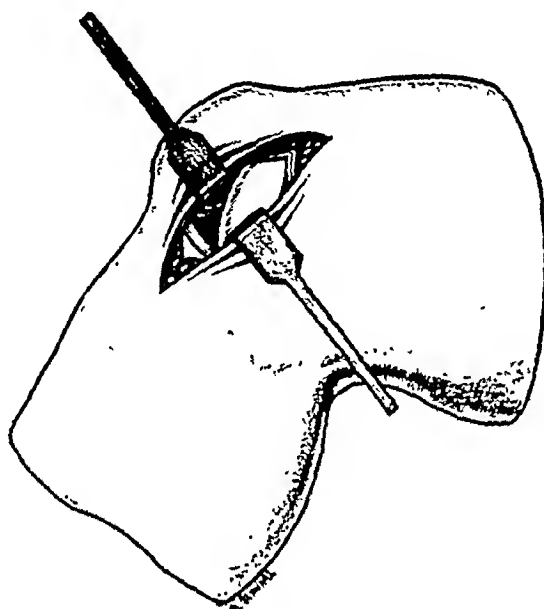


FIG. 3

FIG. 2.—Showing posteromedial "Henderson" approach for removal of entire medial meniscus. This is not always used. The medial collateral ligament is carefully retracted.

FIG. 3.—Lateral parapatella incision to permit visualization of lateral portion of joint and excision of lateral meniscus.

penicillin is instilled. Both the synovium and skin are closed in the arthrotomy incision. As much of the meniscus as possible is removed. A short posterior incision on the medial side will enable one to excise almost the entire medial meniscus. A recent publication by Smillie indicates that the best functional result is obtained by excising the entire meniscus.

Details of this secondary débridement vary somewhat in the different stages of the infected knee:

(1) In the acute septic knee, the menisci usually have not had time to degenerate, and it is impossible to judge their continued viability. Because of the acuteness of the process, it has been thought wise to excise both menisci through medial and lateral parapatella incisions. Although this portion of the operation might be classified as a prophylactic procedure, it is resorted to in an effort to arrest established virulent infection by removing potentially devitalized

structures and such nonresistant tissues as may have already been irreparably damaged by local conditions within the joint.

(2) In the subacute joint, which is usually seen and operated upon somewhat later, degeneration of the menisci may be evident. This is the type of suppurating joint that is most commonly seen when foreign bodies and devitalized articular cartilage remain within the joint. It is the type that responds well to arthrotomy and excision of the menisci. If left untreated, the end-results are almost universally bad. If the meniscus on the side opposite the wound appears normal, it may be left *in situ*. The amount of additional trauma to the joint produced by the removal of the normal appearing meniscus must be weighed against the danger of leaving it within the joint to degenerate subsequently. With minor degrees of reaction within the joint, it seems probable that there is less danger of the viable-appearing meniscus undergoing degeneration at a later time.

(3) With the increased age of the process, the mechanical difficulties of operative intervention are increased. In chronically infected knees, the areas of incision ordinarily are marked by the presence of sinuses, arising from either old incisions or the débrided wound. As previously stated, the operative treatment must be adequate to remove all questionable tissue within the joint. Since the menisci are generally found degenerated at this stage, they must be excised completely. The articular cartilage must be curetted to good bone in those areas where it is necrotic and in the process of degeneration. After the joint has reached this stage of disintegration, it seems likely that it will never be completely painless and that the patient will most probably require resection and fusion of the knee. However, it is possible to arrest the process at this stage and to obtain some motion of the joint, by thorough débridement. Case No. 2 under "Supplement," was a patient who had destruction of the contact surfaces of both the medial and lateral condyles of the tibia and femur. Following excision of the menisci and curettage of the destroyed cartilage, the superficial wounds drained for a few days, but when heard from some ten months after return to the Zone of Interior, he had healed and stayed healed, with 10° to 15° of motion of the knee. Those patients who have not developed destruction of the articular cartilage may be expected to obtain good motion and essentially normal knees. The removal of the completely devitalized meniscus seems to give no lasting disability. It is true that no complete follow-up is available, but the condition of the patients at the time of evacuation would lead one to this conclusion.

Analysis of Operative Results.—Infection, the most dreaded of knee complications, was seen in 29 of the entire series of 244 compound injuries of the knee joint. The criteria used for judging a knee to be infected were, generally, those signs and symptoms described under the heading "Clinical Manifestations of Infected Knees." These cases also showed purulent exudate within the joint, and sometimes the culture was positive for staphylococci or streptococci. Most of these joints had had penicillin instilled, and the absence of

bacteria on culture may possibly be attributed to this fact, as well as the lack of facilities for extensive anaerobic analysis.

Of the 29 infected joints, 15 were explored, using as a basis for treatment the principles of reparative surgery outlined under the heading "Treatment of the Infected Knee." In 14 of the 15 explored patients, the infectious process was eliminated by débridement, including excision of the menisci, closure of the joint, and instillation of penicillin. The one patient who did not respond to the treatment continued to suppurate because of the presence of osteomyelitis of the femoral condyle. Both menisci were removed in eight of the 15 arthrotomies. The lateral meniscus alone was removed in five instances, and the medial meniscus was excised as part of the operative procedure in two cases.

Thirteen of the 15 explored knees subsided promptly, and had some degree of painless motion when evacuated to the Zone of Interior. One of the remaining two patients subsided after a few days and has remained healed for ten months. The one real failure is discussed at more length later.

Of the 29 infected joints, 14 were not subjected to operation. The 14 "unexplored" patients were judged not amenable to arthrotomy and débridement of the joint. Thirteen of the 14 cases had extensively comminuted fractures within the joint and débridement was considered impracticable.

When the comminution is extensive, or when large fragments are broken free and lie within the joint, operative revision becomes a formidable procedure. It has been found that débridement of a comminuted joint will result in operative removal of so much of the joint or articular surface that the articulation can no longer be functional. Furthermore, with removal of the fragments as a part of the secondary débridement, later resection for fusion will result in excessive shortening of the extremity.

Occasionally, in the severely fractured and infected knee, resection of the joint must be done early in order to save life. If the infection permits, on the other hand, it is better to resort to the old type of treatment, and simply drain the joint. Usually in this type of case the soft-tissue damage is so extensive that open drainage is easily maintained. The extremity is immobilized in a plaster hip spica. By such a method, the patient generally can be spared the most serious systemic consequences of a pyarthrosis. By localizing the infection to the joint space, one hopes that the multiple, loose, comminuted fragments of the condyle will become revascularized and solidify. If it is possible to postpone the resection and fusion until such time as this occurs, the operation may be carried out with minimal shortening of the leg.

Four of the infected knee joints regarded as inoperable, insofar as attempting to save the joint was concerned, were subjected to early resection. This type of resection is done frequently by French surgeons and consists, in brief, of excision of the cartilaginous portions of the femur and tibia and approximation of the denuded cancellous ends of the two bones. The French surgeons, with whom we have talked, give Ollier credit for having popularized this operation. It is technically an easy procedure. Usually, the patient with a severe suppurating joint, exhibiting cachexia, weight loss, and anemia,

responds well to this type of therapy. The four patients who were subjected to resection are reviewed briefly.

TABLE I

Total number of compound knee joints treated.....	244
Total number of infected knee joints.....	29
Number possibly infected but not definite.....	8
Total secondarily débrided by method described.....	15
Cases judged irreparable (not explored).....	14
Irreparable cases which were resected and fused.....	4

An American soldier had loss of the lateral condyle of the tibia and extensive loss of soft-parts over the lateral side of the knee. It was impossible to close the joint even by a flap. This patient was blind, and it was thought unwise to delay resection because of the possibility of severe infection which might necessitate amputation and deprive him of such proprioceptive powers as the fused leg might afford.

An American soldier had a partial resection of a completely destroyed knee joint as a part of his primary care in the Evacuation Hospital. As a further complication, he had a dead extremity on the opposite side, secondary to popliteal artery division. The resection of the joint was done to control severe local infection.

The third patient was one with severe fracture, loss of soft-parts, and a virulent superimposed infection. The joint was resected early in an attempt to control the infection. Unfortunately, he developed osteomyelitis of the resected tibia and a spreading infection up the posterior fascial planes of the thigh. The limb was then amputated. This man had extensive periosteal stripping of the tibia, and this was felt to be a large factor in his lack of resistance to bone infection.

The fourth resected case was one with minimal fracture who was seen so late that the joint was destroyed. His prolonged suppurative process had debilitated him to such an extent that immediate resection seemed indicated. His history is presented in more detail in the "Supplement," Case No. 3, since it shows the hazards of inadequate early care of compound injuries of the knee.

TABLE II

Type of Case	Operation		Disposition to Zone of Interior	Total
	Resection	Amputation		
Irreparable because of fracture and infection.....	1	0	5	6
Irreparable because of fracture, infection and open joint..	2*	2	3	7
Irreparable because of prolonged infection but with minimal fracture.....	1	0	0	1
Total irreparable, infected joints.....	4*	2	8	14

* One was later amputated.

Thirteen of the 14 cases judged unsuitable for attempt at operative revision had severe fractures which complicated the operative procedure to such an

COMPOUND INJURIES OF KNEE JOINT

extent that a functional joint could not be expected. The one patient with irreparable joint damage but minimal fracture has been discussed. It is impossible to save all knee joints in warfare because of the frequent serious nature of the complicating fracture and avulsion of soft-parts. Seven of the 14 irreparable knees had such extensive loss of soft-parts that flap closure was either impossible or resulted in failure when tried.

Two amputations were performed in the series of 14 and, in addition, one patient's leg was amputated after the operation of resection. The infection in this case was not controlled by resection. It was the only one in which resection failed to control infection and the amputation was resorted to as a life-saving measure.

Another case coming to amputation was a patient with a previous amputation below the knee and with an open joint and severe condylar fracture. When first inspected, he had a dirty, necrotic knee joint, and reamputation was performed in the lower thigh. One patient, with thigh amputation for gas gangrene, was not considered an amputation for uncontrolled infection of the knee joint.

The remaining eight patients with infected, open joints were relatively afebrile and comfortable when returned to the Zone of Interior for definitive care and probable fusion. They were treated according to the generally accepted methods for suppurating joints, and all will probably have stiff knees, or may end up with operative fusion. In every case, the joints were open and draining.

Eight of the cases (Table I) are listed as possibly infected, but it was impossible to judge accurately. Occasionally, the infection may be so low-grade that it escapes detection. This is apt to be the case more often in the highly comminuted joint. Sometimes, the infectious process is eliminated spontaneously. Due to the tactical situation, a few cases were evacuated before they could be definitely assessed.

The results in those patients upon whom operative intervention was tried in order to arrest suppuration are tabulated in Table III.

TABLE III

Total compound joints.....	244
Total infected joints.....	29
Total joints explored for infection.....	15
Successful elimination of infection by operation.....	14
Unsuccessful elimination of infection by operation.....	1

In all, 15 patients with suppurative arthritis of the knee joint were subjected to arthrotomy, débridement, and closure. Fourteen of these cases were successfully relieved of the infectious process within the joint. The response to operative intervention was usually prompt and gratifying. The effusion subsided rapidly so that in two or three days it was often difficult to aspirate anything from the joint before instilling penicillin. Periarticular swelling persisted for a few days, but the temperature gradually fell as the

effusion subsided. Motion of the knee was encouraged as soon as pain and tenderness permitted. Lack of pain was found to be a very good index of the proper time to institute motion. Almost all the patients had a fair range of painless motion when evacuated.

The one patient upon whom the operative treatment failed had a wound of the popliteal space. Débridement and formal arthrotomy had been done in the forward area, but an anterior approach had not revealed the foreign body or the articular cartilage damage. When he reached the Base, he had a subacute suppurative arthritis. Shortly after admission, the foreign body

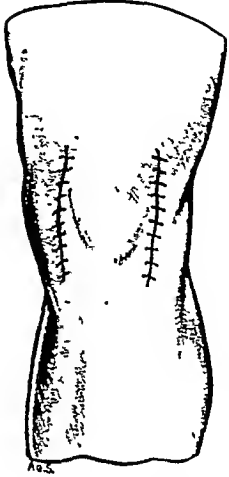


FIG. 4.—Anterior view of joint showing sutured medial and lateral parapatella incisions. (Synovium also sutured.) Posteromedial sutured wound not shown.

was removed, and the area about the damaged cartilage was débrided. The joint continued to suppurate and was reopened in order to remove the menisci and curette the area on the medial posterior femoral condyle. At this operation it was observed that the area of osteomyelitis had enlarged. After this second procedure, he continued to run fever, and the joint was painful and distended. It was necessary to resort to the open joint method of drainage. Foreign bodies in the posterior part of the joint are frequently difficult to find, and surgeons called upon to treat those injuries should be well-acquainted with the anatomy and surgical approaches to the knee joint, recently reviewed by Abbott and Carpenter. The foreign body and cartilage damage could have been easily reached at the time of débridement had a posterior, or Henderson, incision been used.

Table IV is a summary of the 15 patients upon whom operative intervention was undertaken.

Case 9 presents some interesting details. This patient had an infected bullet wound, which in our experience is rare. Also, he seemed to have an infected knee joint, without cartilaginous damage. However, in repeated notes, it was stated that he had little, if any, pain on motion of the knee, and the diagnosis of suppurative arthritis was questionable. He did have prolonged fever and pus was aspirated from the suprapatella region. The joint was finally explored by a lateral approach, and a walled-off abscess of the suprapatella pouch was encountered. Since the knee was contaminated by the procedure, the lateral meniscus was removed to lessen the hazards of infection.

Case 15 was evacuated before the full extent of the response to treatment could be judged. The patient was one with acute manifestations and was still slightly febrile when evacuated. It is possible that he should not be included in this series.

DISCUSSION.—Admittedly, the criteria for established infection within the knee joint are not absolute, since it was impossible to obtain carefully controlled laboratory studies on all the patients treated. Positive cultures were obtained from most of the knees, however, although clinical abstracts fre-

COMPOUND INJURIES OF KNEE JOINT

TABLE IV

Days After
Wounding Until
Arthrotomy or

Case No.	Missile	Bony Injury	Primary Care	Secondary Care	Findings and Procedure	Result
1.	SF*	Pen. fract. lat. condyle of femur and incomplete fract. of patella	Formal explor. Arthrotomy	10	Infected patella curetted. Excision medial meniscus and curette lat. condyle of femur	Healed
2.	SF	Shaft of femur, with with extension into knee	Formal explor. Arthrotomy	12	Infected fracture reduced. Excision of both menisci	Healed
3.	SF	Pen. injury of post. med. fem. condyle, with retained foreign body	Formal explor. arthrotomy	21	Osteo. about foreign body. Excision of both menisci and curettage of the medial femoral condyle	Healed
				31 (reoperated)	Osteo. progressive. Joint left open	Septic
4.	SF	Fract. lat. cond. of femur	Débrided. No formal arthrotomy	10	Excise part of loose lateral condyle. Excision of lat. meniscus	Healed
5.	SF	Fract. lateral condyle of femur	Débrided. No F.A.	7	Excision of part of lat. condyle. Excision lateral meniscus	Healed
6.	SF	Pen. fract. med. condyle of femur	Débrided. No F.A.	10	Excision of both menisci. Débride and curette condyle	Healed, 20° of motion
7.	SF	Lateral condyle of femur about half avulsed	Débrided. No F.A.	8	Ant. cruciate severed. Lat. Condyle of femur loose and removed. Excision of both menisci	Healed
8.	SF	Fract. lower one-third femur, with secondary compound knee	Débrided. Joint inspected	45	Both menisci necrotic and excised. Articular cartilage curetted at points of contact	Healed
9.	Bullet	Minimal cartilage injury to femoral condyle	Débrided. No F.A.	8	Excision lat. meniscus. Had a localized abscess in suprapatellar pouch	Healed
10.	SF	Commin. fract. of upper tibia. Chip fract. of patella	Débrided. No F.A.	6	Curette patella. Excise both menisci. Slide-flap to close joint	Healed
11.	SF	Fract. med. tibial condyle. Retained foreign body	Débrided. No F.A.	13	Remove F.B. excision lateral meniscus. Curette tibial plateau	Healed
12.	SF	None	Débrided. No F.A.	13	Excision of medial meniscus. Removal F.B. in suprapatellar pouch	Healed
13.	SF	Medial tibial condyle	None	6	Excision lat. meniscus curette tibial condyle. Remove foreign body	Healed 60° of motion
14.	SF	Upper tibia	Débrided.	60	Excision of both degenerated menisci. Curette all areas of articular cartilage contact	Healed
15.	Not a battle casualty	None	None	3	Grease and dirt in compound injury sustained in auto accident. Excision both cartilages	Healed

* Shell fragment.

quently have failed to record the report. The clinical evaluation based on temperature, pain on motion, local tenderness, gross appearance of the joint, the character of the joint fluid and, most important, inspection of the interior of the joint, must be accepted as the basis of the report.

Criteria for arrest of the joint infection have been established. Most of the patients have been followed long enough to demonstrate some degree of painless motion, freedom from fever and general systemic improvement.

The excision of the menisci would seem to be an innocuous procedure, insofar as later function of the uninfected joint is concerned. Whether the altered conditions of suppuration within the joint at the time of meniscectomy may affect the ultimate functional result is not known.

In the acute suppurative joint, when the menisci still appear viable, removal of these structures may be questioned. The decision to remove them was made after observing the necrotic menisci in the more chronically infected joints. There can be no doubt that a meniscus is very susceptible to suppuration within the joint. The acute suppurative joint is a serious and formidable problem that calls for the most vigorous measures. Temporizing and trusting that the menisci will remain viable, have not been a part of this operative scheme.

It is recognized that some of the patients, although spared the hazards of suppuration, will have disability that may require future reconstructive procedures. Those with partial loss of a condyle, or with serious ligamentous injury of the knee, may even have to have their knee joints fused. In these patients it can be claimed only that they have been spared the debilitation and hazards of chronic suppuration. Some of the "cured" knees have cartilaginous defects in important weight-bearing areas that may predispose to difficulty. In spite of these facts, it is our belief that the patients have been given the best chance to obtain a serviceable knee joint.

SUPPLEMENT

Case 1.—American officer wounded, August 16, 1944, in Southern France by shell fragments. Due to the tactical situation at the time, he was evacuated to a hospital ship without treatment. On the ship, wounds of the right forearm and thigh were débrided the day after injury. The missile that had penetrated the right knee was not disturbed.

He reached the 21st General Hospital, August 22, 1944, (six days after wounding), with a swollen, tender knee and a temperature of 102°. Motion was not excessively painful, but the joint was hot. Roentgenograms showed a chip-fracture of the patella and a foreign body embedded in the articular surface of the tibia. A formal arthrotomy was performed under a cuff tourniquet on the day of admission. The joint was explored through a medial parapatella incision. There was seropurulent fluid in the joint. The foreign body was extracted, and the defect in the tibial condyle curetted. The medial meniscus was found partly torn, and it was excised. An area of cartilaginous injury on the lateral side of the medial femoral condyle was trimmed. The synovium and skin were closed, with the injection of 20,000 units of penicillin.

The postoperative course was smooth, with rapid subsidence of fever. Motion was started eight days after arthrotomy. He had 60° of motion when discharged to the Zone of Interior.

COMPOUND INJURIES OF KNEE JOINT

Case 2.—American soldier, wounded at Anzio Beachhead, February 20, 1944, by shell fragments. He sustained a penetrating wound of the left thigh, with a comminuted fracture of the femur. The left knee was compounded at the fracture site. The wound was débrided 20 hours after injury at an Evacuation Hospital and a plaster hip spica applied. He arrived at the Base, February 23, 1944, fairly comfortable. On February 25, 1944, the encasement was removed and the extremity placed in skeletal traction. The wounds were not sutured because they did not look clean. On March 6, 1944, (two weeks after wounding) the temperature was 102°F. A diagnosis of a subacute infected knee was made. According to the accepted policies at that time, he was treated conservatively, and the fracture site drained; this, in turn, drained the knee joint. He continued to run a low grade fever. Repeated drainage of the fracture site was performed. In each instance, the knee joint was shown to connect with the fracture site and to contain pus.

Finally, on April 6, 1944, just six and one-half weeks after wounding, the joint was opened widely in order to test the new concepts of reparative surgery on a case of established knee joint infection. The program of penicillin plus reparative surgery had been introduced some two weeks before this time at this hospital.

At operation, both menisci were found devitalized. The points of contact between articular surfaces of tibia and femur, and also between femur and patella, were found in various stages of autolysis. All devitalized tissue was excised and curetted. The joint was then closed and penicillin instilled. The fracture site was fixed by four screws and drained dependently. Because of the multiple incisions and the superficial infection, it was impossible to follow with certainty the state of infection within the joint. However, in retrospect, it seems that it subsided promptly, since only blood could be obtained from the knee joint on repeated aspirations. Instilled penicillin did not leak from the joint. Incisions were almost fully healed when he was discharged, and ten months later, reports from the Zone of Interior indicated that healing was complete.

Case 3.—American soldier, wounded in France, October 31, 1944, by shell fragments, sustained multiple wounds of the chest, abdomen, both arms, and both legs. He was treated at a Field Hospital 30 hours after injury by resection of a segment of the jejunum and primary anastomosis; débridement of all wounds and irrigation of a penetrating wound of the right knee with the installation of penicillin.

A pyarthrosis of the right knee developed. Thirteen days after injury he was transferred to an Evacuation Hospital, where, on the day following admission, he was subjected to formal arthrotomy and the foreign body removed. On November 23, 1944, the joint was explored for the second time, and the medial meniscus removed. On November 27, 1944, he was transferred to the 21st General Hospital where conservative therapy was tried because the joint was open and draining. It became evident that the patient was losing ground. He was extremely emaciated, with an anemia that required repeated blood transfusions. There was loss of appetite and progressive weight loss.

On December 10, 1944, under ether anesthesia, an arthrodesis of the right knee was performed, excising the patella and resecting the cartilaginous portions of the tibia and femur. A few days following resection he began to gain weight, and continued to improve until evacuated January 30, 1945.

The bony damage was slight, consisting of a penetrating type of injury to the femoral condyle.

SUMMARY

1. An analysis of 29 infected knee joints is presented. These cases represent the total infected knee joints in a series of 244 compound injuries of the knee.
2. Because of the high incidence of complications resulting from the use

of traditional methods of therapy in suppurative arthritis of the knee joint, a more active plan of treatment was developed.

3. The clinical manifestations and gross pathology of the acute, subacute, and chronic stages of infectious arthritis of the knee are presented.

4. An active operative approach to these cases is outlined, with the elimination of all devitalized and potentially devitalized tissue within the joint, the closure of the synovial cavity and skin, and the local use of penicillin.

5. Arrests of the infectious process was obtained in 14 of 15 cases operated upon according to these principles.

6. Case histories are presented.

REFERENCES

- ¹ Abbott, L. G., and Carpenter, W. F.: Surgical Approaches to the Knee Joint. *J. Bone and Joint Surg.*, 27, 277, 1945.
- ² Churchill, E. D.: Surgical Management of the Wounded in the Mediterranean Theater at the Time of the Fall of Rome. *ANNALS OF SURGERY*, 120, 268, 1944.
- ³ Lyons, Champ: Penicillin Therapy of Surgical Infections in the United States Army. *J. A. M. A.*, 123, 1007, 1943.
- ⁴ Phemister, D. B.: Changes in the Articular Surfaces in Tuberculosis and in Pyogenic Infections of Joints. *Amer. J. Roentgen.*, 22, 1, 1924.
- ⁵ Smillie, I. S.: Observations on the Regeneration of the Semilunar Cartilages in Man. *Brit. J. of Surg.*, 31, 398, 1944.

SURGICAL MANAGEMENT OF GUNSHOT WOUNDS OF THE PELVIC VISCERA AND THEIR LATE COMPLICATIONS*

LT. COL. GEORGE BENTON SANDERS, M.C.
LOUISVILLE, KY.

AND
MAJOR IAN G. HODGE, M.C.
LANCASTER, PA.

FROM THE SURGICAL SERVICE, VAUGHAN GENERAL HOSPITAL, HINES, ILLINOIS

PERFORATING GUNSHOT WOUNDS of the pelvis are among the most baneful of war injuries. Their high mortality and morbidity are due to the presence of important hollow viscera of several systems which are closely packed into this bony cavity, any, or all, of which may be irreparably damaged by the passage of a missile. To this may be added the shock of the bony damage itself which, although not of a degree comparable with that attending fracture of the bones of the lower extremities, nevertheless, remains an important added insult.

Statistical studies in clinical surgery are often misleading. Nowhere are they more so than in the surgery of warfare. As Morgan has most aptly stated: "It is unwise to draw too many conclusions from the study of wounded at the Base, since the Forward Surgeon alone knows of his failures and disappointments; the survivors tell only of the triumphs."

It is well, therefore, to bear this in mind when reviewing the following statistics.

According to Sandrey and Mogg, who surveyed a large series of cases from World War I, the incidence of bladder wounds in warfare is comparatively rare; namely, about one in every 3,000 or 4,000 battle wounds. However, according to these authors, wounds of the bladder constitute as much as 5 per cent of all abdominal wounds. The same authors give the incidence of associated pelvic fracture in cases of bladder wounds as over 50 per cent, and state that associated injury to the rectum occurs in over 33 per cent of bladder wounds. In a series of 53 cases of wounds of the bladder from the World War I, surveyed by Fullerton, the incidence of associated pelvic fracture was given as 42 per cent. Changing technics of warfare, and especially the evolution of the land mine as a weapon of defense, has, according to first reports, increased the incidence of injury to the pelvis and its viscera, especially during certain phases and campaigns of the recent war. Table I, based on necessarily incomplete reports, is only an approximation of what is to be expected from the completed statistical surveys of this conflict.

Wounds of the ureter are said to be statistically rare. In World War I, only two cases of ureteral wounds were reported from a study of a large number of abdominal wounds in the British Expeditionary Force. Young was able to discover only four cases of ureteral injury in a similar survey made on casualties from the American Expeditionary Force. Most authors, British and

* Presented at the Surgical Conference, Sixth Service Command, Chicago, Illinois, 1945.

American, who have discussed the subject, admit, however, that the incidence must be much higher since many cases are either overlooked, or die of more severe associated visceral injuries. Kimbrough in a recent study of 237 consecutive injuries to the genito-urinary tract has reported eight cases of ureteral injury. It must be emphasized again, however, that these figures were compiled from the hospital records of rear echelon installations and are, therefore, subject to the misleading influences of sampling and selection.

TABLE I
INCIDENCE OF ASSOCIATED BONY PELVIC INJURY
IN WOUNDS OF THE PELVIC VISCERA

Location	Fracture of Pelvis
Deep urethra.....	20%
Bladder*.....	45-60%
Colon and rectum.....	55%
Combined injuries, both systems.....	65%

* Wounds of bladder, with or without bony injury, are associated with wounds of the colon or rectum in 45-70% of the cases.

The viscera most often injured in compound gunshot fractures of the pelvis fall naturally into four main groups: First, organs of the gastro-intestinal tract; namely, the cecum, sigmoid, rectum and, lastly, the terminal ileum, which is injured so often, like an innocent bystander in all types of gunshot injuries in this region. Second, the genito-urinary organs; the deep urethra, bladder, and juxtavesical portions of the ureters. Third, combined injuries of the above two systems, which occur in the following order of frequency: rectum and urethra, rectum and bladder, sigmoid and bladder, and sigmoid and left ureter. (Cecal and right ureteral injuries are rare, although one was encountered on the Surgical Service of this hospital.) Fourth, injuries to the great vessels and nerves of the pelvis.

Of these injuries due to gunshot wounds, those of the deep urethra, bladder, rectum, and sigmoid, although *usually* caused by the missile, may be produced by indriven bony fragments from the pelvis, in which case they are almost always extraperitoneal. The remainder, including the combined injuries, are nearly always due to the missile itself. In the present war the missiles causing these injuries are more often fragments of high explosive shell or bomb casing than rifle or machine gun bullets, in the ratio of about 3 to 1. The former show a high percentage of retention within the tissues of the pelvis, the latter often make a complete perforation and exit from the body.

PRIMARY SURGICAL MANAGEMENT

Proper surgical management of these injuries in the forward areas is exceedingly important, not only for the saving of life, but for the reduction of morbidity and the prevention of distressing complications which will require extensive and elaborate surgery later. Adherence to, or deviation from, fundamental surgical principles is directly reflected in morbidity figures and in the necessity for future surgery involving sacrifice of tissues and organs.

In general, it may be said that the early surgical care of these cases embraces the following four cardinal principles: Recognition; repair; diversion; and drainage.

Recognition.—It is, by now, a surgical aphorism that every wound of the buttock, perineum, upper thigh, or hip, should be considered as penetrating the abdomen unless it can be conclusively demonstrated otherwise. Even at celiotomy, however, early recognition, not only of the presence, but of the type, extent, and multiplicity of injury may be exceedingly difficult, especially in extraperitoneal injuries of the rectum and ureter. Reconstruction of the track of the missile should aid in detection of concealed damage, the most valuable manifestation of which is extravasation of blood or urine. The possibility of progressive infarction of the intestinal wall, with subsequent perforation distinct from the main rent, should always be kept in mind, as emphasized by Shaw Dunn, in 1917.

In practically all cases of gunshot wounds of the pelvis, an attempt should be made to pass a catheter into the bladder. Cystography and cystoscopy have been advocated, but are often not feasible in forward areas, and are not without danger. Excretory urography, if available, is valuable, especially in the diagnosis of ureteral injury.

Repair.—In wounds of the colon, exteriorization is the procedure of choice, but is not always feasible in the case of injury to the fixed portions of the colon. Suture repair of urinary and colonic defects is of the utmost desirability in wounds of the bladder and of colonic segments that cannot be exteriorized. The fear of later bowel stenosis should not inhibit thoroughness in repairing colonic defects unsuitable for exteriorization since a complementary proximal colostomy should always be done.

In urethral injuries, primary suture is desirable only if the lesion is readily accessible. With injuries to the deeper portions of the urethra, approximation of the torn ends by combined manipulation, both retrograde and from below, with immobilization of the segments by a catheter splint, is the simplest and most desirable treatment. As a general rule, primary suture repair is not often practical for the ureteral injuries of warfare. However, if the injury involves the distal end of the ureter, an immediate ureterovesical transplant is recommended. In higher ureteral injuries, if recognized early, a simple closure which does not unduly constrict the ureter is sometimes feasible.

Diversion.—Efficient diversion of the fecal or urinary flow is an essential corollary. In wounds of the cecum and ascending colon, ileocolostomy, with resection or repair of the damaged right colon, is the ideal advocated by many, which is rarely achieved, while exteriorization, slightly less than ideal but still efficient, is too infrequently attempted and too often inadequately done. Cecostomy, which has been most frequently employed, has proved very disappointing in the prevention of late complications in the cases that have been reviewed at this hospital, and its value of an emergency measure seems to leave much to be desired. Wounds of the transverse colon are easily exteriorized. In injuries of the left colon, exteriorization in the form of a proper colostomy seems to be the procedure of choice, and often, of necessity. Failing this, and especially in

wounds of the pelvic colon too low to exteriorize, diversion seems to us most ideally obtained by means of an adequate defunctioning colostomy of the Devine or double-barrelled spur-type, made no lower than the transverse colon, a point which, although originally mentioned by Lockhart-Mummery and Cuthbert Wallace, has been insufficiently stressed to date. In injuries of the urinary tract either at, or distal to, the bladder, a suprapubic cystotomy should always be done. It is of the utmost importance that the suprapubic drainage tube emerge from the bladder at or near the junction of the anterior and superior aspects of that organ and that the direction the tube follows through the abdominal wall be upwards and anteriorly so that it emerges at a point midway or higher, between the umbilicus and symphysis pubis.

Cutaneous ureterostomy or nephrostomy have been advised as emergency measures in certain ureteral injuries but, to date, we have seen no cases in which this was done or in which we believe such treatment was indicated primarily.

Drainage.—Adequate free drainage of all extraperitoneal injuries, actual and potential, and of all tissue planes opened-up by dissection is an absolute "must." In the repair of injuries involving the bladder, the extravescical spaces must be adequately drained. In injuries to the urethra, perineal drainage should be instituted if there is any suspicion of extravasation. With ureteral lesions, adequate and free drainage of the retroperitoneal tissues by means of a soft rubber tube, capable of maintaining urinary drainage, should be instituted and the drain allowed to remain in place until urinary drainage has ceased. In colonic injuries, the omission of drainage, especially of extraperitoneal injuries, most frequently results in the lethal "colon septicemia" described in the first World War, or, if the patient survives this, troublesome abscesses and complex fecal fistulae develop. The most difficult problems in drainage are those associated with colonic injuries near the bottom of the rectovesical pouch in which a decision must be made whether to drain transperitoneally by the suprapubic route or extraperitoneally from below *via* the perirectal space.

LATE COMPLICATIONS

The late complications of these injuries of the pelvic viscera with which we are most concerned in general hospitals in this country, include: Obstruction; fistula; stricture; urinary tract lithiasis; and infection. Of these, the management of fistulae, whether fecal, urinary, or combined urinary-fecal, interests us most at this time. A detailed discussion of the problems and methods of attack on such fistulae is not germane to this report. Certain principles will be presented which have seemed of importance to us concerning the surgical management of persistent fecal fistulae from the large bowel, and of urinary-fecal communications or fistulae. The management of the other complications listed is similar to that employed in civil practice and has been dealt with adequately by many writers on the subject.

Fecal Fistula.—We feel strongly that older methods of dealing with persistent fecal fistula, involving dissection and excision of the track down to the

opening in the bowel, which is then closed through what is often an inadequate operative incision, are unsatisfactory. With the advent of succinylsulfathiazole, a more radical transperitoneal attack on the origin of the fistula in the bowel wall, including excision of the indurated margins of the bowel defect, resection of the involved colonic segment if necessary, and thorough layer-suture of the bowel, as in an elective anastomosis, can be safely undertaken, and has been our personal choice in 15 cases. Adequate mobilization of the bowel is imperative, neglect of which may result in failure of the closure. Reinforcement of the suture line with an omental flap or graft is highly desirable. The fistulous track itself may then be either excised, curetted and packed, or even left to obliterate spontaneously.

TABLE II

Fecal Fistula:

(1) Spontaneous closure the rule if:

- (a) Fistula is tortuous.
- (b) Fistula does not traverse bone, abscess or granulomatous mass.
- (c) Efficient defunctioning colostomy is present proximally.
- (d) Bowel defect is not large.
- (e) Obstruction is absent distally in the bowel.

If above favorable conditions are lacking, direct attack often must be made to close colonic defect by suture.

(2) Direct attack on fistula necessitates:

- (a) Efficient debacterIALIZATION of involved colon—(succinylsulfathiazole, and/or favorably placed and adequately defunctioning colostomy).
- (b) Freedom from obstruction distally in the large intestine.
- (c) Freedom from active infection adjacent to fistula.

Urinary-Fecal Communications.—In combined injuries to the gastro-intestinal and genito-urinary tracts, urinary-fecal communications commonly develop which present interesting problems to the surgeon and urologist. With careful analysis, a rational, staged-attack may be planned, with, in many instances, resulting conservation of tissues and organs, and the cure of the fistula without undue danger to the patient.

It has appeared to us that the primary consideration in preparing these patients for surgical cure of such a complex fistula is the establishment of a thoroughly efficient defunctioning colostomy well proximal to the involved segment of bowel. Hardly less important is the provision and maintenance of adequate urinary decompression or drainage.

The choice and location of the colostomy for fecal diversion is important. We prefer a Devine-type of colostomy made in the right transverse colon, for all lesions distal to the splenic flexure. A completely divided type of colostomy, with the two limbs brought out of the abdomen at a short distance from each other, is fully as efficient as the Devine colostomy, and permits a more anatomic reconstruction of bowel and abdominal wall at the time of closure. Tangential or loop-colostomies are not efficient exclusion procedures. In the case of fistulae involving the right hemicolon, we feel that an end-to-side ileotransversecolostomy is preferable to cecostomy.

With the establishment of fecal diversion and adequate urinary drainage, many urinary-fecal communications appear to close spontaneously, but will

reopen upon restoration of the fecal stream. In two of our cases, closure of a sigmoid colostomy resulted in the reopening of previously closed ureterocolic and vesicocolic fistulae. Permanent cure resulted in each after the establishment of a Devine colostomy followed by transperitoneal closure of the communication.

In two other cases from our series, fistulae between the right ureter and ascending colon apparently closed following end-to-side ileocolostomy. The permanence of closure was never estimated because extensive urinary infection, lithiasis, and renal damage necessitated right nephrectomy in both. In these two cases, both admitted to our Service with such severe renal damage that the necessity for nephrectomy was obvious, the problem arose as to whether to do the nephrectomy first, or to exclude the right hemicolon by ileocolostomy as a preliminary measure. In each case, a communication existed between the ureteropelvic junction and the ascending colon. Feeling that the nephrectomy incision would involve the colonic defect, it was decided to perform ileocolostomy as a preliminary measure in each. Spontaneous closure of the communications apparently resulted, and subsequent nephrectomy was performed without incident and without the feared wound infection. Permanent cure of the external portion of the fecal fistula, however, required right hemicolectomy in each case.

Damage to the ureter is usually so extensive in ureterocolic fistulae, that intractable ureteral stricture results even after successful closure, making nephrectomy mandatory. For this reason, it is usually the procedure of wisdom not to attempt to preserve the involved kidney but to accomplish the cure of the fistula by nephro-ureterectomy. Our experience with this interesting complication is, admittedly, limited to three cases, in two of which nephro-ureterectomy was done. In the third case, however, which will be presented later, it was possible to eradicate the fistula by a transperitoneal attack, and to preserve the kidney.

TABLE III

Urinary-Fecal Communications:

(1) Requirements for closure:

- (a) Adequately defunctioning colostomy favorably placed.
- (b) Adequate diversion and/or drainage of urinary flow.
- (c) Freedom from distal obstruction in both systems.

Under the above conditions spontaneous closure of the urinary portion of the defect often occurs, but reopening will occur if adverse conditions of infection and/or obstruction supervene later.

(2) Fecal end of communication usually needs direct surgical attack even after spontaneous closure of urinary portion. Requisites for efficient and permanent operative closure of colonic portion of fistula are:

- (a) Freedom from active infection (abscess, cellulitis) adjacent to fistula.
- (b) Defunctioned, debacterialized bowel.
- (c) Direct suture of colonic defect, or resection of involved colonic segment.
- (d) Interposition of omental or peritoneal flap if possible.

If a direct attack is necessary on either the ureter or the bladder to close such a fistula, adequate urinary drainage must be carefully maintained. In the case of ureteral lesions, a temporary ureteral splint in the form of a ureteral catheter may be used for the first few days if it is watched carefully. Adequate drainage of soft-tissue planes for possible leakage must be maintained.

GUNSHOT WOUNDS OF PELVIC VISCERA

PRESENTATION OF CASES

Of some 106 cases of perforating wounds of the abdominal viscera admitted to the surgical service of Vaughan General Hospital there were 45 cases of gunshot wounds of the pelvic viscera requiring reparative surgery at this hospital. Of the latter, 14 were associated with compound fracture of the bony pelvis (Table IV).

Of six cases with ureteral injury admitted to this hospital, two were associated with compound fracture of the pelvis, a high incidence, since in warfare usually the upper ureter is the site of injury and the bony pelvis escapes damage. Of these six cases, only two were discovered at overseas installations, one at the Base, 2.5 months after wounding; the other at the Front at the time of the primary operation, 13 hours after wounding. The remaining four were disclosed during routine preoperative studies on the Surgical Service of this hospital, three to four months after the initial combat injury.

TABLE IV
SITES OF INJURY IN 14 CASES OF COMPOUND PELVIC FRACTURE,
WITH VISCERAL DAMAGE DUE TO MISSILE

Location of Bony Injury	Location of Visceral Injury
1. Ala of right ilium	Ascending colon
2. Ala of right ilium	Cecum
3. Ala of left ilium	Terminal ileum, sigmoid
4. Sacrum	Bladder, sigmoid, terminal fifth of left ureter
5. Sacrum	Rectum and bladder
6. Ala of right ilium	Ascending colon, cecum, terminal ileum
7. Ala of left ilium	Left sciatic nerve
8. Sacrum	Terminal fourth, left ureter
9. Ala of left ilium	Sigmoid, terminal ileum, jejunum
10. Ala of left ilium	Ileum
11. Sacrum	Rectosigmoid
12. Horizontal rami, both pubes	Penile and membranous urethra
13. Ascending and descending rami, left ischium	Anus and rectum
14. Right femoral head and acetabulum	Bladder

Of these 14 cases, the following five have been selected as showing most clearly some of the important points in surgical treatment which have already been discussed.

ILLUSTRATIVE CASE REPORTS

Case 1.—H. Z., age 25, was wounded in Germany by a sniper bullet which entered the abdomen *via* the left lower quadrant and exited through the left iliac region causing in transit a compound fracture of the left ilium, multiple perforations of the jejunum and ileum, and a complete transection of the sigmoid colon. At operation, 11 hours later, the perforations in the ileum were closed, ten inches of jejunum were resected with end-to-end anastomosis, and the severed ends of the sigmoid were brought out of the abdomen, as a colostomy, through a stab incision in the left lower quadrant. Postoperative course was uneventful except for drainage and sloughing of tissue from a sinus in the débrided wound of exit.

On admission to Vaughan General Hospital, June 8, 1945, the patient presented the following: A well made sigmoid colostomy in the left lower quadrant. An inflammatory

mass, the size of a grapefruit in the left iliac fossa, completely occluding the distal limb of the colostomy. A large fistulous track, passing through the mass and through a defect in the ala of the left ilium, with its external opening in the wound of exit, its internal opening in the distal limb of the colostomy about one inch below the skin surface. Pressure on the mass caused thick pus to well-out of both ends of the fistula (Fig. 1).

Course in Vaughan General Hospital: On July 3, 1945, a Devine colostomy was made in the right half of the transverse colon, followed seven days later by wide incision and drainage of the mass in the left iliac fossa. Shortly thereafter, the mass decreased rapidly and had practically disappeared 16 days postoperatively. The fistula remained open. Since it was wide, short, and traversed bone close to its source in the bowel, direct attack was thought necessary for permanent cure of the fistula. After resection of the involved segment of colon, with end-to-end anastomosis, a procedure particularly adapted to a bowel defunctioned by a Devine colostomy, permanent healing resulted. The Devine colostomy was closed four weeks later without incident.



FIG 1.—Case 1: The abscess in the iliac fossa is outlined on the skin. The skin discoloration over the abscess can be seen. Pointers are in the internal and external openings of the fecal fistula which traverses the ala of the left ilium. The colostomy is rotated 90°.

COMMENT.—This case illustrates the inadequacy of a defunctioning colostomy placed close to the site of original injury in the bowel, and emphasizes the point that elective colostomy, in cases of injury to the pelvic bowel and viscera, should be made no lower than the transverse colon. In this case, of course, the exteriorization colostomy in the sigmoid was the choice of necessity and not of election, but it might have been wiser at the time to complement this with a proximal transverse colostomy.

Case 2.—V. N., age 21, was wounded in action in the Philippines by a sniper bullet on April 2, 1945. The bullet entered the abdomen anteriorly through the right lower quadrant near the midline, tracked backward and slightly upward, and exited in the right flank posteriorly, causing a compound fracture of the ala of the right ilium and a perforating wound of the ascending colon in transit. At operation, four hours later, a débridement of the wound of exit was performed, the abdomen was opened through a lower right rectus incision, excising the wound of entrance, and the rent in the extraperi-

toncal portion of the ascending colon was closed by suture. The site of injury was drained through the right flank and a simple cecostomy was done. Postoperative course was fairly uneventful, but the patient developed a fecal fistula at the site of injury to the colon which drained intermittently through both the wound of exit and the drainage wound in the right flank. The patient began to have daily bowel movements per rectum about one month after operation. The cecostomy continued to drain a moderate amount of semiliquid feces.

The patient was admitted to Vaughan General Hospital, May 12, 1945, at which time he presented the following: A simple cecostomy in the right lower quadrant draining a small amount of feces intermittently. Two fecal fistulae, one in the right lumbar region, the other in the right flank, passing through the ala of the right ilium, and both communicating with each other at their common origin in the ascending colon.

Large rubber catheters could be passed into the colon with ease through both fistulous openings. Barium enema showed the defect in the colon as a large tent-like process of bowel which had been drawn into the defect in the ilium. On July 19, 1945, a thorough closure of the cecostomy was done extraperitoneally. The peritoneum was then opened, the ascending colon and cecum mobilized and the colon was detached from the ilium, revealing an extraperitoneal rent in the bowel, about 5 cm. in its longest diameter, which had been drawn in purse-string fashion into a large bony defect in the ilium about the size of a silver dollar. There was evidence of chronic osteomyelitis of the ilium. The bowel defect was repaired with a two-layer suture, a flap of omentum was reflected over the suture line and interposed between the bowel and the bony defect, and the area was thoroughly drained extraperitoneally through the right flank.

Postoperative course was uneventful, with the patient ambulatory on the first postoperative day, normal bowel movements the second postoperative day, regular house diet the third postoperative day. On the eighth postoperative day, the patient developed signs and symptoms of partial small bowel obstruction near the ileocecal junction, and a mass, the size of an orange, could be felt in the right lower quadrant. He was again subjected to operation and an abscess containing about 60 cc. of creamy pus was drained extraperitoneally in the right lower quadrant. Exploration of the interior of the abscess cavity revealed no communication with the bowel but traced its origin back to the area of osteomyelitis in the right ilium. After this, the patient did exceedingly well, continued to have normal bowel movements by rectum; the abscess cavity closed promptly, but the patient continued to drain a moderate amount of pus from the sinus in the right iliac region overlying the area of osteomyelitis. The fecal fistulae, however, remained closed. Consequently, about one month later, a sequestrectomy of the right ilium was performed, removing four moderate-sized bony fragments and excising the surrounding diseased bone. Complete healing of the wound was obtained 12 days later. During the past six months, he has suffered no recurrence of infection or drainage (Figs. 2, 3, 4, A and B).

COMMENT.—This case demonstrates the inadequacy of cecostomy as a diverting mechanism for perforations of the right colon. An excellent demonstration of the fact that a fecal fistula traversing bone cannot be expected to heal spontaneously.

Case 3.—G. O., age 35, was wounded in Italy by a fragment of high explosive shell on June 3, 1944. The fragment perforated the sacrum just to the right of the midline, tracked anteriorly and to the left and did not exit. At celiotomy, done 24 hours later, four perforations of the rectosigmoid and one of the bladder were found and sutured and a proximal sigmoid colostomy was performed. An indwelling urethral catheter was inserted into the bladder and catheter drainage of the bladder was continued for the following month. After removal of the catheter, the patient had no urinary difficulty.

One month later, he was admitted to Vaughan General Hospital in good condition.



FIG. 2.—Case 2: The fracture site in the right ilium is poorly shown.

I. V. pyelograms demonstrated only dilatation of the lower two-thirds of the left ureter and failure of visualization of the terminal 4 cm. or the left ureter. There was no hydronephrosis. Shortly after admission the patient developed left ureteral colic and at about this time, urinary drainage into the distal loop of the colon was demonstrated and corroborated by the injection of indigo-carmin. Cystoscopy and retrograde urography revealed a stricture of the left ureter in its terminal portion, with fairly advanced left hydronephrosis and hydroureter. Three stones were disclosed in the left ureter just above the stricture. Under conservative management, with ureteral catheter drainage and repeated dilatation of the ureter, all stones were passed and the hydronephrosis receded. The sacral sinus of entrance, which had drained intermittently up to this point, was injected with lipiodol and connection with both rectosigmoid and left ureter was



FIG. 3.—Case 2: Barium enema, showing colonic origin of fecal fistulae, one of which traverses ala of right ilium.

GUNSHOT WOUNDS OF PELVIC VISCERA

demonstrated. A subsequent period of two months of conservative management ensued, during which time the patient's general condition improved remarkably, he gained 25 pounds in weight and the sacral sinus ceased to drain. At this time, all studies indicated closure of the ureterosigmoid and sacral fistulae. After an additional eight weeks of waiting, the sigmoid colostomy was closed. For two weeks thereafter, the patient's convalescence was uneventful. At the end of this time, however, the sacral sinus reopened and drained pus. Studies revealed the reopening of the urinary-fecal communication. A Devine colostomy was then done in the right half of the transverse colon. Shortly after this, the sacral sinus again ceased to drain. One month later, studies revealed closure of the urinary-fecal communication, but the sacral sinus could still be demonstrated communicating with the rectosigmoid. On April 17, 1945, the pelvis was explored transperitoneally, and the rectosigmoid was found to be adherent to the anterior wall of the

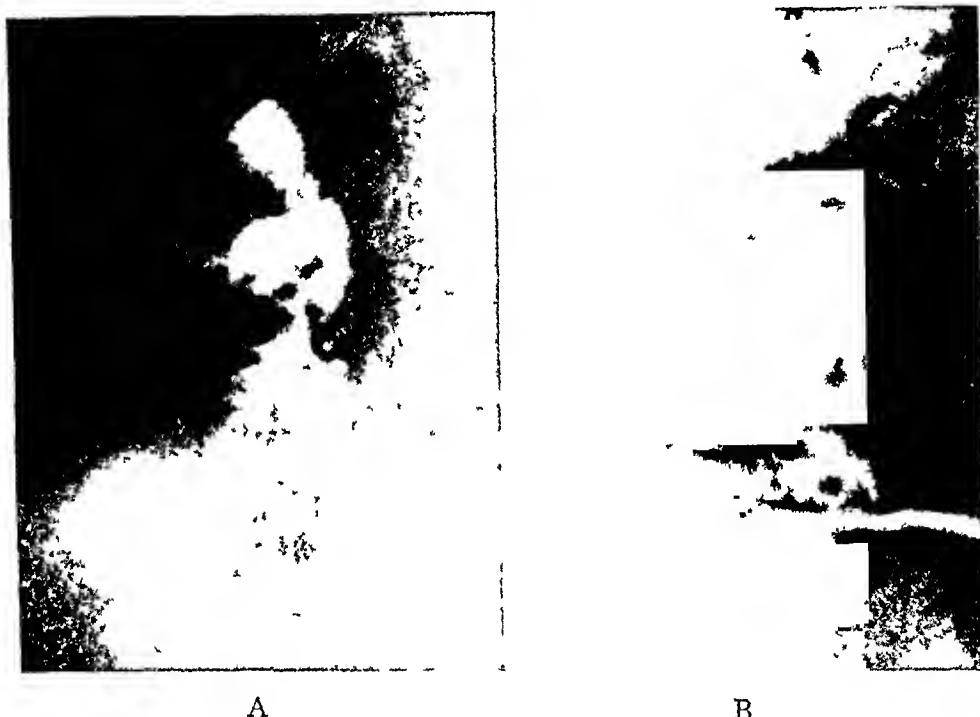


FIG. 4.—Case 2: Two views of lipiodol injection of both fecal fistulae, showing persistence despite cecostomy. Note approximation of the two catheters introduced through the two divergent external fistulae, meeting at common origin of the fistulae in the ascending colon.

sacrum and to the juxtavesical portion of the left ureter. A small tent-like process of bowel wall was drawn into the defect in the bone. The rectosigmoid was thoroughly mobilized and peeled off the sacrum and left ureter, disclosing a small rent in the posterior wall of the bowel and exposing the outer coats of the ureter. The lumen of the ureter was not opened in the dissection. The rent in the colon was carefully closed and oversewed, and a pedicle flap of omentum was interposed between the bowel and the sacrum and ureter.

The patient's postoperative course was uneventful, the sinus closed thoroughly and permanently, subsequent studies revealed little evidence of ureteral stricture and no evidence of hydronephrosis, infection, or lithiasis. On June 22, 1945, the Devine colostomy spur was crushed and the fecal stream reestablished. Closure of the persistent tiny stomas of the Devine colostomy was done under local anesthesia four weeks later. For the past nine months, all studies have failed to demonstrate the recurrence of any fistulous opening, and the patient is in excellent condition, having gained 55 pounds, in all, during

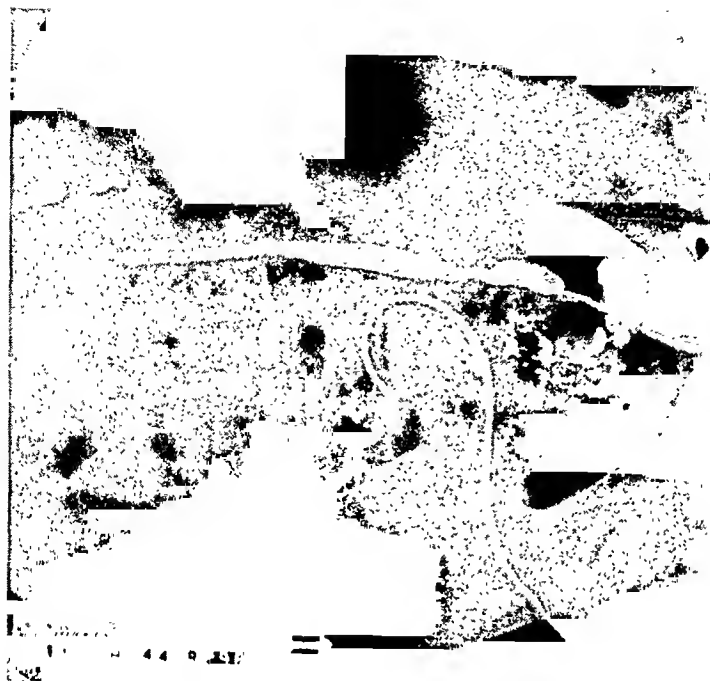


FIG. 6.—Case 3: Lipiodol injection of sacral opening of ureterosigmoid fistula, showing sigmoid and ureteral connections. This incomplete pyelogram was obtained by lipiodol injected solely through the sacral opening. Note ureteral calculus just above stricture in left ureter.



FIG. 5.—Case 3: Retrograde pyelogram, showing degree of hydronephrosis, secondary to stricture, and ureterosigmoid fistula.

GUNSHOT WOUNDS OF PELVIC VISCERA

this period. Recent pyelograms show a normal kidney, pelvis and ureter on the left, with the exception of a slight narrowing at the site of the former fistula. There is no urinary tract infection as far as can be determined (Figs. 5, 6 and 7).

COMMENT: The ureteral injury was overlooked at the primary operation. Here is a typical instance in which the making of a colostomy below the transverse colon, in a case of pelvic injury, has interfered with subsequent



FIG. 7.—Case 3: Retrograde pyelogram done after operative cure of the ureterosigmoid fistula.

reparative surgery. This case demonstrates very well that fecal fistulae traversing bone do not heal spontaneously and, also, that with proper deflection of the fecal stream, the urinary component of a urinary-fecal fistula tends to close spontaneously.

Case 4.—A. K., age 21, was struck by a fragment of high explosive shell on January 29, 1945, which entered the left iliac region, tracked through the ala of the left ilium and penetrated the abdomen, where it was retained in the extraperitoneal tissues of the pelvis. A conservative débridement of the wound of the hip was done, the abdomen opened and a large extraperitoneal hematoma of the left iliac fossa was evacuated. Fearing that the blood supply of the distal colon was impaired, a proximal sigmoid colostomy was done. A fragment of shell was removed from the pelvis but a similar fragment retained in the tissues of the left iliac region was not recovered. Shortly after operation, the presence of a partial left sciatic nerve palsy was discovered.

The postoperative course was somewhat stormy, but the patient was evacuated to the United States and admitted to Vaughan General Hospital on March 27, 1945. On admission, the patient was extremely emaciated, cachectic, and suffering from marked anorexia. He was running a hectic type of temperature and presented in addition to the partial sciatic palsy on the left; a large draining sinus of the left iliac region; and chronic osteomyelitis of the left ilium, with a large (3x4-cm.) sequestrum visualized roentgenologically in the ala of the left ilium. A large abscess cavity was discovered in the pelvis which communicated with the sinus in the left iliac region. After preliminary supportive measures, patient was operated upon, April 12, 1945, at which time



FIG. 8—Case 4. Lipiodol injection of pelvic abscess through iliac sinus. Note retained fragment of shell-casing, large sequestrum in ala of left ilium.

an incision was made parallel to the crest of the left ilium and about two inches below it, encircling and removing the sinus track. The sequestrum, which involved the margin of the greater sciatic notch, and which lay against the left sciatic nerve and iliac vessels, was removed along with a handful of pulped necrotic bone. The pelvic abscess cavity was then easily entered through the bony defect and evacuated. A large rubber tube drain was inserted through the rectum into the most dependent portion of the cavity which lay against the posterolateral rectal wall. Immediately after operation, the patient noted that he could move his left foot and leg much more freely than before and in the subsequent seven days, most of the residual findings of the sciatic nerve palsy disappeared.

The patient's postoperative course was essentially uneventful, his appetite returned promptly, his fever dropped in 24 hours and remained normal, and he began to gain rapidly in weight and strength. With irrigations through the tube, the cavity closed rapidly and became obliterated in approximately 14 days. On July 19, 1945, after the

GUNSHOT WOUNDS OF PELVIC VISCERA

patient had been ambulatory for a month and a half, the colostomy was closed, and the remaining fragment of shell was removed from the left iliac region. At present there is only a slight trace of residual sciatic palsy, consisting of minimal atrophy and weakness in the musculature of the leg and thigh. Recent roentgenograms of the left ilium show no evidence of residual osteomyelitis and suggest rapid bony regeneration. All sinuses have been closed for some time (Figs. 8 and 9).



FIG. 9.—Case 4: Roentgenogram of pelvis taken three months after surgical drainage of pelvic abscess through rectum, sequestrectomy, and removal of shell fragment. Residual lipiodol remains from previous injection. Iliac sinus has been healed for six weeks. Note absence of osteomyelitis and beginning bony regeneration in ala of ilium.

COMMENT: Obviously, the primary débridement of the wound of entry and the drainage instituted for the intrapelvic hematoma were inadequate. At the primary operation, with the abdomen open, it should have been relatively easy thoroughly to drain the hematoma extraperitoneally.

Case 5.—H. W., age 30, was wounded by a fragment of high explosive shell on March 31, 1945, which entered the perineum just to the left of the anus, tracked upward along the left side of the rectum and lodged in the left sacral mass at the level of the promontory. At operation, eight hours after the injury, a débridement of the wound of entrance was done, the abdomen was opened and the pelvis explored. No injury to the rectum or bladder was noted but there was evident retroperitoneal hemorrhage. A



FIG. 11.—Case 5: Intravenous pyelogram, showing escape of dye through ureteral defect, into extraperitoneal abscess cavity.

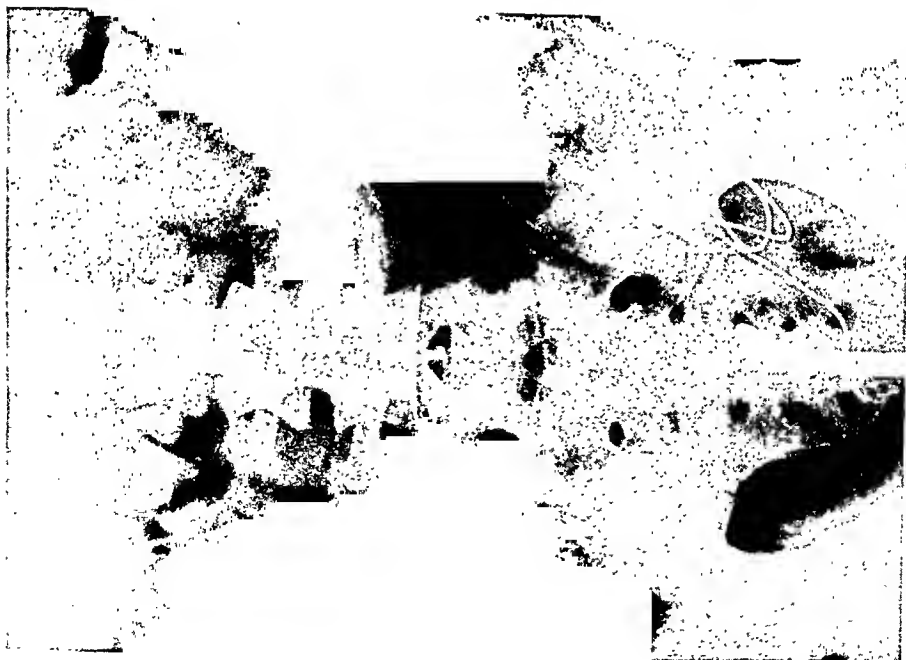


FIG. 10.—Case 5: Roentgenogram showing ureteral catheter escaping through defect in left ureter and coiling up in extraperitoneal abscess cavity.

GUNSHOT WOUNDS OF PELVIC VISCERA

sigmoid colostomy was done. The patient drained profusely both from the wound in the perineum and from the lower angle of the celiotomy incision. This drainage was not recognized as being urine.

The patient's postoperative course was somewhat stormy, but he was finally evacuated to the United States and admitted to Vaughan General Hospital on April 27, 1945. At admission, the abdominal wound was fully healed and the colostomy was functioning well. There was copious drainage of urine through the sinus in the buttock and the voided urine was grossly contaminated. Studies disclosed a large pelvic abscess filled with urine and cellular debris. No injury to the bladder was seen cystoscopically. An ureteral catheter introduced into the left ureteral orifice was found, roentgenologically, to be coiled in this abscess cavity. On May 10, 1945, the sinus track was opened widely and a No. 22 F. catheter introduced into the cavity from below, for free drainage. Gradually, the urine escaping through the perineal sinus decreased and finally stopped altogether. At this point the catheter was removed from the sinus. On July 7, the patient apparently developed a retroperitoneal mass which was thought to be a pelvic abscess. An attempt was made to incise and drain this through the perineum but was unsuccessful. Following this, after many unsuccessful attempts, an ureteral catheter was introduced into the pelvis of the left kidney. Pyelograms revealed only minimal back pressure on the left kidney but showed leakage of the dye in the region of the abscess cavity. It seemed apparent, therefore, that ultimate healing of the defect in the left ureter, in the presence of the residual abscess cavity, was not to be expected and that future stricture formation at this point would eventually destroy the left kidney. Consequently, on August 7, 1945, a left nephrectomy was performed.

Postoperative course was entirely without incident, and the perineal sinus track closed rapidly. Five weeks later, the sigmoid colostomy was closed, also without incident. The patient has remained well since (Figs. 10 and 11).

COMMENT: This case demonstrates the importance of early recognition of ureteral lesions. Had this patient had early adequate drainage, a secondary ureteral repair, or anastomosis into the bladder might have been done without the development of the large abscess cavity. With secondary infection, such a procedure was never possible. Further, the colostomy opening, situated as it was high in the left lower quadrant, greatly hindered surgical approach to either the left kidney or the left ureter.

SUMMARY

Due to the close association of viscera and organs of several systems within the pelvis, gunshot injuries of this region are among the most severe of war injuries. The pelvic fracture itself is relatively insignificant compared to the lethal potency of injuries to its contents.

The primary surgical management of these injuries, guided by the principles of prompt recognition; thorough repair; efficient diversion of urinary and fecal currents when necessary; and adequate drainage at all times, is of paramount importance, not only for the saving of life, but for the prevention and minimizing of distressing complications later.

Deviation from fundamental surgical principles in the early surgical care of gunshot injuries to the pelvis and its viscera results in increased mortality and morbidity, and in the necessity for further elaborate surgery, involving sacrifice of tissues and organs, with added risk to the patient.

Surgeons charged with the primary care of these injuries should be alert

to the possibilities of concealed extraperitoneal damage to the bladder, recto-sigmoid, and ureters. Injuries to the ureters are most often unrecognized at the time of primary operation when an unparalleled opportunity exists for the preservation of the associated kidney.

Proximal colostomies should divert and defunction, as well as decompress. Cecostomy is not an efficient diverting or defunctioning procedure.

The proper location of a proximal colostomy should take into consideration the likelihood of further reconstructive surgery upon the distal bowel. In wounds of the pelvic colon, especially, it may be wiser to place the colostomy no lower than the transverse colon, and to perform a complementary transverse colostomy along with exteriorization of a damaged pelvic colon.

Persistent fecal and urinary-fecal fistulae, particularly those traversing bone, require a direct attack for permanent closure, which is most satisfactorily done transperitoneally upon a bowel defunctioned by an efficient proximal colostomy. Following efficient fecal diversion, spontaneous closure of urinary-fecal communications often occurs provided urinary decompression or drainage is maintained, and urinary tract infection kept to a minimum. Reopening of such an apparently closed urinary-fecal communication commonly follows restoration of the fecal current indicating that direct attack on the fistula is necessary in the majority of cases for permanent cure.

The histories of five illustrative cases are presented.

BIBLIOGRAPHY

- Coffey, R. C.: Remote or Indirect Subperitoneal Drainage in the Extraperitoneal Closure of Persistent Fecal Fistulae. *ANNALS OF SURGERY*, 45, 827, 1907.
- Colcock, B. P.: Traumatic Perforations of the Colon as Seen in a General Hospital. *Surgery*, 17, 1, January, 1945.
- Deaver, J. B.: The Traumatic Abdomen. *ANNALS OF SURGERY*, 68, 275, 1918.
- DeBakey, M. C., and Carter, B. N.: Current Considerations of War Surgery. *ANNALS OF SURGERY*, 121, 545-563, May, 1945.
- Dixon, C. F., and Deuterman, J. L.: The Management of External Intestinal Fistulas. *J. A. M. A.*, 111, 2095, 1938.
- Dunn, J. S., and Drummond, H.: Ulceration of the Colon in the Neighborhood of Gunshot Wounds. *Brit. Jour. Surg.*, 5, 59-65, 1917-18.
- Everidge, John: Injuries of the Ureter. *Brit. Jour. Urol.*, 12, 234, 1940.
- Fullerton, Andrew: Observations on Bladder Injury in Warfare: A Study of 53 Cases. *Brit. Jour. Surg.*, 5, 248-288, 1917-18.
- Gordon-Taylor, G.: Complicated Injuries of the Urinary Tract. *Brit. Jour. Urol.*, 12, 1-28, 1940.
- Gordon-Taylor, G.: Second Thoughts on the Abdominal Surgery of "Total" War: A Review of over 1,300 Cases. *Brit. Jour. Surg.*, 32, 247-258, October, 1944.
- Heyd, C. G.: The Increasing Usefulness of the Devine Colostomy in Left Colon and Rectal Surgery. *ANNALS OF SURGERY*, 116, 913, 1942.
- Lewis, D., and Penick, R. M.: Fecal Fistulae. *International Clinics*, Vol. I, Series 23, 111, 1933.
- Lichtman, A. L., and McDonald, J. R.: Fecal Fistula. *Surg. Gynec. & Obst.*, 78, 449, May, 1944.
- Lockhart-Mummery, J. P.: Discussion on Methods of Making and Closing Colostomy Openings. *Proc. Roy. Soc. Med.*, (London) 10, 135, 1916-17.

- Marshall, S. F., and Lahey, F. H.: The Surgical Treatment of Abdominal Fistulas. New Eng. Jour. Med., 218, 211, 1938.
- McCague, E. J., and Semans, J. H.: The Management of Traumatic Rupture of the Urethra and Bladder Complicating Fracture of the Pelvis. Jour. Urol., 52, 36-41, 1944.
- Morgan, C. N.: Wounds of the Colon. Brit. Jour. Surg., 32, 337, 345, January, 1945.
- Morgan, C. N.: Wounds of the Rectum. Surg. Gynec. & Obst., 81, 56-62, July, 1945.
- Neligan, G. E.: War Injuries to Genito-urinary Tract. Brit. Med. Jour., 2, 291, 1939.
- Ogilvie, W. H.: Abdominal Wounds in the Western Desert. Surg. Gynec. & Obst., 78, 225, March, 1944.
- Ogilvie, W. H.: Forward Surgery of Abdominal Wounds. Lancet, 246, 555, 1944.
- Poth, E. J., and Knotts, F. L.: The Clinical Use of Succinylsulfathiazole. Arch. Surg., 44, 208, February, 1942.
- Poth, E. J.: Succinylsulfathiazole and Phthalylsulfathiazole in Surgery of the Colon. Surgery, 17, 773, June, 1945.
- Reynolds, J. R.: War Injuries to the Genito-urinary Tract. Jour. Urol., 53, 419-421, February, 1945.
- Ross, J. C.: Injuries of the Urinary Bladder. Brit. Jour. Surg., 32, 44-49, July, 1944.
- Sandrey, J. G., and Mogg, R. A.: Wounds of the Bladder. Lancet, 1, 716-720, June, 1944.
- Senn, Nicholas: The Etiology, Pathology and Treatment of Intestinal Fistulae and Artificial Anus. Am. Jour. Obst., 3, 321, 1894.
- Uhle, C. A. W., and Erb, H. R.: Reconstruction of the Membranous Urethra. Jour. Urol., 52, 42-59, 1944.
- Wallace, Cuthbert: A Study of 1,200 Gunshot Wounds of the Abdomen. Brit. Jour. Surg., 4, 679-778, 1916-17.
- Wallace, Cuthbert: The Lettsomian Lectures on War Surgery of the Abdomen. Lancet, 1, 56, 596, 633, 1917.
- Walter, C. F., Rollinson, H. D., Jordon, A. R., and Bank, A. G.: Five Hundred Emergency Operations for Abdominal Wounds. Lancet, 1, 207, 1917.
- Young, H. H.: Wounds of Urogenital Tract in Modern Warfare. Jour. Urol., 47, 59-108, 1942.

Dr. George B. Sanders
1417 Heyburn Bldg.
Louisville 2, Kentucky

STUDIES ON THE ACID DÉBRIDEMENT OF BURNS*

MARION B. SULZBERGER, M.D., ABRAM KANOF, M.D.,

AND

RUDOLF L. BAER, M.D.

NEW YORK, N. Y.

THERE IS GENERAL AGREEMENT that the early removal of the nonviable tissue or slough has a beneficial effect in most third-degree burns and in many other forms of necrotic wounds. It is also agreed that the optimum procedures for removal of nonviable tissue must be: (1) as gentle, nondamaging and "nonshocking" as possible; and (2) as "selective" as possible (*i.e.*, must remove the nonviable tissue and leave unharmed all the viable elements).

In recent years many investigators have devoted their efforts to the development of chemical methods which would remove slough more gently and more selectively than any available surgical or mechanical method. In 1940, Glasser¹ reported success in removing slough by the application of a proteolytic compound. Cooper, Hodge, and Beard² made a similar report in 1943, and Howes,³ in the same year, suggested digestion of the slough by treatment with hydrochloric acid and pepsin. But these methods are generally rather slow, and the semidigested material offers a medium for bacterial growth. There is also reason to believe that these methods are not sufficiently selective and that some viable as well as nonviable tissue is proteolized, thus, helping to convert second-degree burns into third-degree lesions.

In 1944, Connor and Harvey⁴ described a new method of slough removal. These authors reported that by their method, the slough was removed rapidly and selectively by the separation of large, membranous segments along a line of cleavage between the dead and the viable cells. The agent used by Connor and Harvey was *pyruvic acid in a water-starch gel* and their experimental work was done chiefly on dogs.†

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College.

We wish to express our gratitude to Dr. Milton C. Winternitz, Admirals Ross T. McIntire and Harold W. Smith and Dr. David P. Barr for their advice and cooperation.

The statements in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

† Lam and Puppenthal working on experimental burns in dogs reported that cotton wet with distilled water was as effective in removing slough as pyruvic acid in starch paste (*ANNALS OF SURGERY*, 121, 866, June, 1945). It was not the purpose of our studies to compare the effects of wet compresses with other methods, as our objective was the development of an effective gel for field use. However, the data presented in the present report demonstrate that acid had a beneficial effect, as shown by the figures on comparative efficacy of "blank" starch paste *versus* the same paste containing pyruvic acid.

Because the Connor-Harvey method showed great promise, and because the topical treatment of burns formed a very substantial problem in war medicine, Division 5 and the Subcommittee on the Treatment of Infected Wounds and Burns of the Committee on Medical Research of the Office of Scientific Research and Development requested the present authors to undertake further studies of the new technic.

These studies had four major objectives:

(1) To compare the effect of the method developed by Connor and Harvey with the effect of other methods in the topical therapy of standard third-degree burns in human subjects.

(2) To elaborate a more practical vehicle to replace the starch paste gel, which is impractical, as it is unstable and must be freshly prepared each day.

(3) To find a more stable and more generally available acid to replace the pyruvic acid which is unstable and difficult to obtain in large quantities.

(4) To extend the sphere of knowledge regarding the technic, complications, advantages, disadvantages, and mechanisms of the new method.

The results of our experiments were reported in a series of 16 classified communications to the National Research Council. The wartime restrictions now being lifted, the purpose of the present report is to summarize our results and to present them in a form which will facilitate further trial of the method.

EXPERIMENTAL

Under authorization of the Secretary of the Navy, and other responsible authorities, the tests were performed on several hundred young male volunteers at the U. S. Naval Disciplinary Barracks at Hart's Island, New York.

Paired comparisons were used throughout. Two symmetrically situated areas, one on the flexor surface of each forearm, were burned in all subjects. The comparative efficacy of two treatment agents was then tested by applying the agent under study to one of these burns; and applying another agent, *i.e.*, the standard control material, in identical fashion to the sister burn on the opposite arm. The sites were then observed daily; and the day on which débridement took place, and later, the day of complete epithelization, was noted.

This method eliminates errors caused by the great differences in healing rate which occur in different individuals, in different skin areas, or which may be due to different diets and to many other factors. Moreover, it has been estimated (John Fertig, Columbia University, personal communication) that results based on healing rates obtained in a series of six men by this method, (where the effects of a new agent are estimated by comparison with the effects of a common standard control agent in the same individual) are often statistically as valid as results obtained by observing the healing rates of 50 burns treated with a new material without reference to the effects of a standard control treatment in the same individual.

In the earlier experiments, the burns were produced by the application of an accurately measured amount of liquid mustard gas. Previous experience with mustard gas had enabled us to develop a technic by which lesions of about

similar size and depth could be produced. These burns were approximately 4.0 cm. by 2.5 cm. in size. Excision and histologic examination of the burned areas showed that the lesions were largely third-degree burns, but with occasional islands of intact epithelial elements (usually pilosebaceous; at times sweat glands?) within the third-degree area.

Later experiments were conducted with thermal burns. These were produced with an apparatus designed and built by A. H. Moritz and F. C. Henriquez, of Harvard University. With this apparatus we applied to the skin a round copper disk 1.0 cm. in diameter at a temperature of 67° C. for 60 seconds. (The constant temperature was maintained by the apparatus in which the disk forms the bottom of a container in which methanol is *kept* boiling (temperature 67° C.) by passing an electric current through a high resistance wire in the walls of the container). No pressure was used except that exerted by the weight of the applicator itself. Histologic examinations showed that the resulting lesions were full-thickness third-degree burns with few glandular rests.

As a rule, the débriding applications were begun on the third, fourth or fifth day after the thermal burns, and on the seventh day after the mustard gas burn. This interval was allowed to elapse in order to permit some diminution of the early exudation. The medication was then applied in identical manner to all sites in all subjects. A tablespoonful (approx. 10.0 cc.) of the acid-containing agents or of the blank vehicle controls was applied to each lesion; the materials were immediately covered with a 2- x 2-inch square of gauze. This was covered with one or two layers of vaselined gauze to retard drying out. The vaselined gauze was, in turn, covered with dry gauze which was held in place by two wide strips of Elastoplast (Duke). This cover was made more air-tight by sealing the edges and seams with ordinary adhesive plaster. The agent was applied daily, the applications being continued until débridement took place in all the men of the series; or until further applications in a particular individual had to be stopped because of a prohibitive degree of irritation. On the average, débridement took a total of four to five days for a thermal burn; and eight to ten days for a chemical burn. When the débriding agent was discontinued, both lesions, with the exceptions noted in Table I, were treated identically. The postdébridement treatment was almost always a sulfonamide cream (5 per cent sulfadiazine, sodium sulfadiazine, sulfanilamide, or sulfathiazole), applied daily under a gauze dressing until epithelization was complete.

A. THE SEQUENCE OF EVENTS DURING ACID DÉBRIDEMENT

With the best agents, débridement of the thermal burns usually took place after the third or fourth application of the acid, *e.g.*, on the sixth to eighth day of the burn. In lesions which were about to débride, the slough turned yellowish-brown on the second day; a line of separation became visible at the periphery on the next day; and soon after the slough lay loose or almost loose, in the wound. These loose sloughs often came off "spontaneously" as the dressing was removed (Fig. 1), but more often they were held by a few

ACID DÉBRIDEMENT OF BURNS

strands and were lifted off with a forceps (Fig. 2). With the slough off, a clean granulating base was generally disclosed.

It was observed early that the ulcer resulting from acid débridement of the slough was larger than an undébrided control lesion. This increase in size was especially noted when K-Y jelly was the vehicle for application of the acid. However, the scar which subsequently formed at the site of an acid-débrided burn, while slightly larger, was *smoother and more elastic* than that on undébrided lesions (Fig. 3).



FIG. 1



FIG. 2

FIG. 1.—Successful removal of slough. Status at 13 days after application of mustard gas.

Right arm: Sodium sulfadiazine 5 per cent ointment applied at two days after contamination and reapplied daily.

Left arm: No treatment until 7th day; then pyruvic acid-starch paste applied daily for six days, at which time slough came off in one piece. (Slough shown lying on piece of gauze below ulcer on left arm.)

FIG. 2.—Chemical burn after seven applications of pyruvic acid in starch paste. The slough is ready to be lifted off as a membrane, revealing a clean base.

Another observation was the exceedingly small incidence of infection in these wounds. They were handled daily in an ordinary prison room, without the usual appurtenances or precautions for surgical sterility. Still, in over 1,500 lesions produced and treated, there was no serious or general infection, and only two or three arms developed a slight cellulitis and required hot soaks for a day or two. This is a far cry from the experience related by Lee and Rhoads⁵ that they have never seen a third-degree burn treated with tannic acid which did not eventually develop an infection.

A follicular dermatitis of the surrounding normal skin, usually mild but *sometimes severe*, frequently followed the application of the acid. However, the dermatitis regularly cleared up within a few days after the discontinuance of the acid. It never seemed to interfere with healing except where the higher concentrations of acid, later to be discussed, were used.

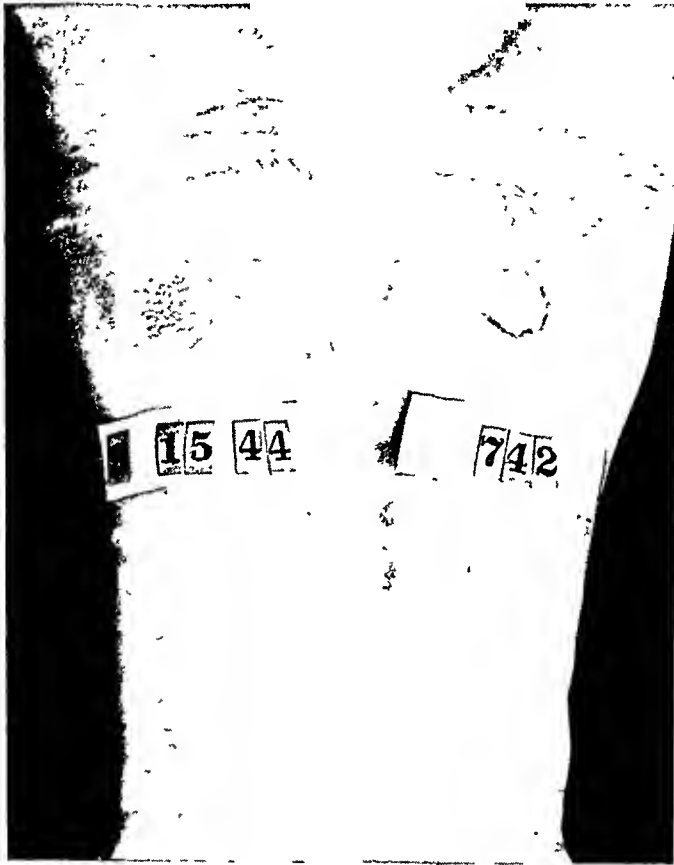


FIG. 3.—Two equal chemical burns. The left arm was treated daily with sulfadiazine cream. The right arm was left untreated for seven days, then débrided with pyruvic acid in starch paste. At one month the right lesion is completely epithelized while the left still shows considerable slough.

B. COMPARISON BETWEEN HEALING TIME AFTER ACID DÉBRIDEMENT AND HEALING TIME WITH OTHER TREATMENT METHODS

In our first series of experiments, we were able to confirm the finding that application of 0.9 per cent (0.1 molar) pyruvic acid-starch paste* led to

* A 0.1 molar solution of pyruvic acid is prepared by adding 6.8 cc. pyruvic acid (Eastman No. 498) to one liter of distilled water (resulting p_H is 1.9). 80 grams of ordinary cornstarch are suspended in a few ounces of the cold pyruvic acid solution. The rest of the liter of 0.1 molar pyruvic acid is heated to the boiling point and the cold starch suspension is added slowly, with stirring. Heating is continued for a few more minutes and the resulting pyruvic acid-starch paste is allowed to cool. The p_H of the finished gel is 1.8 to 1.9.

débridement of thermal and chemical burns, as described by Connor and Harvey.⁴ Moreover, application to a burn of 0.9 per cent (0.1 molar) pyruvic acid in starch paste daily until débridement took place and then daily dressings with 5 per cent sodium sulfadiazine cream resulted in quicker healing than could be achieved in a similar, symmetrically situated lesion treated as follows: (a) Left untreated; (b) treated daily with "blank" starch paste to which no acid had been added; (c) treated daily with pressure bandages with sodium sulfadiazine ointment; (d) treated daily with pressure bandages with sulfadiazine ointment; or (e) treated daily with pressure bandages with one-third per cent silver nitrate in petrolatum. The results of some typical experiments are shown in Table I. The indicated superiority of the acid débridement method was maintained throughout the entire series of over 1,500 wounds.

TABLE I

No. of Volunteers	Av. Heal. Time on 0.1 M. Pyr. Ac.- starch Paste and Later with Sod. Sulfadiaz. Cream, in Days	Agent Used on Symmetrical Lesion and Average Healing Time, in Days	Type of Burn
11	20.2	No treatment.....	Thermal
10	19.4	"Blank" starch paste	Thermal
13	30.0	"Blank" starch paste	Chemical
4	31.5	5% sod. sulfad. cream.....	Chemical
6	38.1	1/3% silver nitrate in petrolatum.	Chemical
5	31.1	5% sulfad. cream.....	Chemical

C. COMPARISON OF PYRUVIC ACID WITH OTHER ACIDS

As soon as our results confirmed the value of acid débridement with pyruvic acid-starch paste, the next problem was to ascertain whether some other acid could be substituted for pyruvic acid. The question was of great practical importance, for pyruvic acid was difficult to obtain in sufficient quantity and was relatively unstable. The question also had its theoretic importance; while it seemed likely that the action of pyruvic acid might be an hydrogen ion effect which could be duplicated with other acids, the possibility had been suggested that the débridement might be due to properties peculiar to pyruvic acid. We, therefore, tested the action of the following other acids: hydrochloric, mandelic, tartaric, lactic, citric, and phosphoric acids.

Only one of the acids tested was found to be in all ways equal to pyruvic acid. This was phosphoric acid. In concentrations of 0.98 per cent (approximately 0.1 M.) phosphoric acid in starch paste at a p_H of 1.9 to 2.0 was found to débride chemical and thermal burns, and to accelerate their healing as efficiently as did pyruvic acid in starch paste.

Some of the other acids were approximately as effective as pyruvic if they were used in higher concentrations than 0.1 molar. Thus, 0.66 M. mandelic acid, 0.34 lactic acid, 0.2 tartaric acid, and 0.14 citric acid, all in starch paste, débrided the standard burn almost as quickly as did the 0.1 M. pyruvic acid in starch paste. However, the higher concentrations of acids in general produced a prohibitive degree of dermatitis of the surrounding skin. These same

acids in 0.1 M. concentration, *i.e.*, the concentration corresponding to that used with pyruvic acid and not producing excessive dermatitis, were relatively ineffective. Tartaric acid in this low concentration was an exception; at 0.1 M. strength, it was almost, but definitely not quite, as good as pyruvic acid.

Hydrochloric acid, because of its high degree of dissociation, produced a low initial p_H (about 1.9) when used at a concentration of 0.1 M., but was found to be ineffective in producing débridement. We believe that, as suggested by Connor and Harvey, this is due to lack of a reservoir of H. ions sufficient to maintain the low p_H for a long enough period of time.

Thus, our results completely confirm the findings of Harvey and Connor *that not only the original hydrogen ion concentration but the buffer capacity of the acid is important in the achievement of slough removal*. The more weakly dissociated acids have a larger reserve of hydrogen ions, and are able to maintain the low p_H for a longer period of time.

However, at the same molarity there appeared to be differences in the efficacy of different acids. Phosphoric acid 0.1 M. at a p_H of 1.9 was as good as pyruvic acid 0.1 M. at a p_H of 1.9; tartaric acid, 0.1 M. at a p_H of 2.0 and mandelic acid 0.1 M. at a p_H of 2.2 were not as good as pyruvic acid at a p_H of 1.9. Citric acid 0.1 M. at a p_H of 2.0 was inferior, while lactic acid 0.1 M., at a p_H of 2.3, was almost ineffective.

D. COMPARISON OF STARCH PASTE WITH OTHER VEHICLES

Starch paste in water, while an effective vehicle for acids, is a very impractical vehicle. A first drawback is due to the fact that the word "starch" does not designate a single, specific substance, but may refer to a number of powders produced by grinding various grains. Even starches from the same grain vary greatly from lot to lot. In the early experiments in which different brands of starch were used the different series of men frequently evidenced large differences in their rates of débriding and, therefore, in the healing time of lesions treated with pyruvic acid in starch paste. These variations were effectively reduced by buying a large quantity of different types of cornstarch and mixing the various lots to produce a pooled starch of uniform quality which could be used throughout.

But the principal impediment to the general usefulness of starch paste lies in the fact that the preparation of this paste is far too involved to be practical. The procedure is a form of cookery, necessitating not only dilution of the acid, but heating it, adding to it a small quantity of the starch powder and then mixing in the rest of the powder under constant stirring and heating. Moreover, the mixture must be prepared freshly each day. In order to eliminate these drawbacks a systematic series of experiments was begun in the attempt to discover a more suitable vehicle for the acid.

The essentials for a suitable vehicle were outlined as follows:

- (1) It must be chemically compatible with the acids.
- (2) It must facilitate free diffusion and delivery of the acid, for which reason there must be an aqueous outer phase.

(3) It must cause no irritation to the skin, either by itself or in combination with the acid.

(4) It must have no systemic toxicity as a result of absorption when used in the therapeutic quantities and concentrations.

(5) It must have a consistency suitable for application to all parts of the skin.

(6) (a) It must be capable of easy and rapid preparation. (b) It must be, with its contained acid, sufficiently stable and in other ways suitable for distribution and storage in practical packages.

The problem of finding such a vehicle was divided into two large subdivisions. The first was a search for a "ready made" gel vehicle in which the acid was present or could easily be added. The second was the elaboration of an hygroscopic powder containing the acid and other needed ingredients and which would produce a gel suitable for immediate use simply by the addition of water.

E. READY-MADE GELS

In the search for a "ready-made" gel, a total of 61 different formulae were prepared and tested.* On the basis of previous experience and preliminary tests, it was thought that there were two types of materials which could be omitted from further testing: (a) those which were highly irritating on skin test; and (b) those which showed poor diffusion of the acid in "*in vitro*" models.

As each of the 61 formulae could not be tested on actual burns without seriously depleting the supply of volunteers, a method of screening was elaborated by which the more promising formulae could be selected for further definitive testing. The screening skin tests were as follows:

(1) Each proposed material was used as a dressing on a group of normal arms and kept on for 24 hours. At the end of this time the skin was examined for evidence of irritation.

(2) At the same time, together with others, each material was placed as a patch test on the backs of another series of men.

Correlation of the results of these skin tests gave the relative irritancy of a series of materials; and indicated which were too irritating to warrant further trial.

The preparations which were not prohibitively irritating to the skin were then tested in the laboratory to screen for probable efficiency of action. Three types of laboratory tests† were employed to study the *in vitro* diffusion of acid out of vehicles:

* The following pharmaceutical houses participated in the development of these formulations: Bristol-Myers Co., Hillside, N. J., Arthur D. Little, Inc., Boston, Mass., and Norwich Pharmacal Co., Norwich, N. Y. Their coöperation in this work is gratefully acknowledged.

† Lt. George Rosenfeld, U. S. N. R., suggested and carried out these tests. We are grateful to him for his expert assistance which made this phase of our studies possible.

(1) Diffusion of the acid out of the vehicle into a colloidal aqueous gel containing alizarin as indicator. This turned from red to yellow, showing how far the acid had diffused in a given time (Fig. 4).

(2) Diffusion of acid out of the vehicle across a cellophane membrane into water, the p_H of which was regularly tested.

(3) Diffusion of an acid out of a vehicle directly into blood serum, the p_H of which was determined at intervals by submerging Beckman external titration electrodes in the serum layer without touching the vehicle.

These methods have been more fully described in a paper on methods.⁶

The acid-containing preparations which were found satisfactory by the above screening tests were then tested on chemical and thermal burns in human subjects.

RESULTS

As a result of all these tests, the following combinations were found to be equal to 0.1 M. pyruvic acid in starch paste in regard to such essential properties as effectiveness of slough removal, speed of healing produced, and low degree of irritancy:

1. Methyl cellulose—water gels with 0.1 M. pyruvic or phosphoric acid:		
(a) Pyruvic acid.....		6.8 cc.
Methyl cellulose (25 cps.).....		170.0 Gm.
Water.....		821.2 cc.
(b) Phosphoric acid.....		6.74 cc.
(85%—1.71 sp. gr.)		
Methyl cellulose (25 cps.).....		170.0 Gm.
Water.....		818.5 cc.
(c) Pyruvic acid.....		6.8 cc.
Methyl cellulose (4,000 cps.).....		40.0 Gm.
Sorbitol (Arlex).....		10.0 Gm.
Water.....		941.2 cc.
2. K-Y jelly with 0.4 M. pyruvic or phosphoric acid:		
(a) Pyruvic acid.....		27.2 cc.
K-Y jelly (Johnson & Johnson).....		1,000.0 Gm.
(b) Phosphoric acid.....		27.0 cc.
K-Y jelly.....		1,000.0 Gm.
3. Pectin-Ringer's solution—glycerin gel with 0.1 M. pyruvic acid:		
Pyruvic acid.....		6.8 cc.
Pectin.....		30.0 Gm.
Glycerin.....		79.3 cc.
Ringer's solution.....		861.2 cc.

The more than 50 acid-containing preparations which were found to be unsatisfactory need not be listed here. But it may be stated that the unsatisfactory preparations included the following types of vehicles: silica gels, glycerin-starch pastes, methocel-petrolatum-water ointments, Tween-water emulsions, water-in-oil emulsions, vanishing cream-type emulsions and carbowax ointments.

F. POWDERS

In an effort to further simplify the use of the acid method for débridement, experiments were undertaken with dry, hygroscopic powders which contained both the acid and the elements of the vehicle and which needed only the

addition of water to complete the medication, forming gels ready for use in a few minutes. At our suggestion these combinations were developed by Drs. A. M. Mattocks and W. A. Lazier of the Southern Research Institute,⁷ working under an O. S. R. D. contract on the "Treatment of Infected Wounds and Burns." We subjected the gels formed by these powders to the screening methods already described; and the more promising combinations were tested on third-degree burns in human volunteers by the paired comparison technic.

Seven formulae were found to be *almost* (but not quite) as effective as 0.1 M. pyruvic acid in starch paste with regard to both slough removal and shortening of healing time. They were all *better* than the pyruvic acid in starch as regards *lack of irritancy*.

The seven formulae are:

1. Pyruvic acid.....	19. Gm.
Methyl cellulose (4,000 cps.).....	200.
Xynomine.....	40.
Mix two parts of the powder with 15 parts of water. pH of the gel is 1.87.	
2. Pyruvic acid.....	66. Gm.
Methyl cellulose.....	500.
Mix 1 part of the powder with 13 parts of water. pH of gel is 2.0.	
3. Pyruvic acid.....	36.8 Gm.
Methyl cellulose.....	300.
Sorbitol.....	60.
Mix 1 part of the powder with 10 parts of water. pH of gel is 2.2.	
4. Phosphoric acid.....	20. Gm.
Methyl cellulose.....	300.
Sorbitol.....	60.
Mix 1 part of the powder with 10 parts of water. pH of gel is 20.0.	
5. Pyruvic acid.....	26.6 Gm.
Hydroxyethyl cellulose (WS-100).....	300.
Arlacel C.....	75.
Mix 1 part of the powder with 3 parts of water. pH of gel is 2.24.	
6. Pyruvic acid.....	17.8
Hydroxyethyl cellulose (WS-500).....	200.0
Mix 1 part of the powder with 6 parts of water. pH of gel is 2.3.	
7. Phosphoric acid.....	30. Gm.
Methyl cellulose.....	300.
Sorbitol.....	60.
Mix 1 part of the powder with 10 parts of water. pH of gel is 1.79.	

DISCUSSION.—The technic of acid débridement seems to offer a safe, simple and practical method for the topical treatment of third-degree burns. In such experimental burns this treatment produces a clean, pink, granulating base suitable for skin grafting within three to five days after the beginning of treatment.⁴ In the process, areas of viable tissue and areas of "second" and "first"-degree burn which are usually present in all severe cases, are saved to act as centers for reëpithelization. Quick removal of the dead tissue removes a good pabulum for bacterial growth and minimizes the absorption of toxic materials from destroyed tissue. Connor and Harvey⁴ have suggested that in patients with large burns the acid treatment had best be started within two or three days, or as soon as peripheral vascular failure has been controlled. If the patient is first seen after the slough has been present for some time, acid

treatment is best begun immediately. The débriding material should be applied liberally over the burnt areas; for example, about 3,000 cc. for a burn involving the leg, or 6,000 to 8,000 cc. for a burn involving the entire thigh and leg. The adjoining unburnt skin may also be included in the dressing; an excess is safe, while insufficient amounts are ineffective. The medication should be covered with dry gauze, then with "vaselined" gauze, and the whole covered over by large sheets of gauze or linen. The burn is redressed every 24, 48 or 72 hours, depending on the amount of exudation and the rapidity of the drying out of the acid-containing preparation.

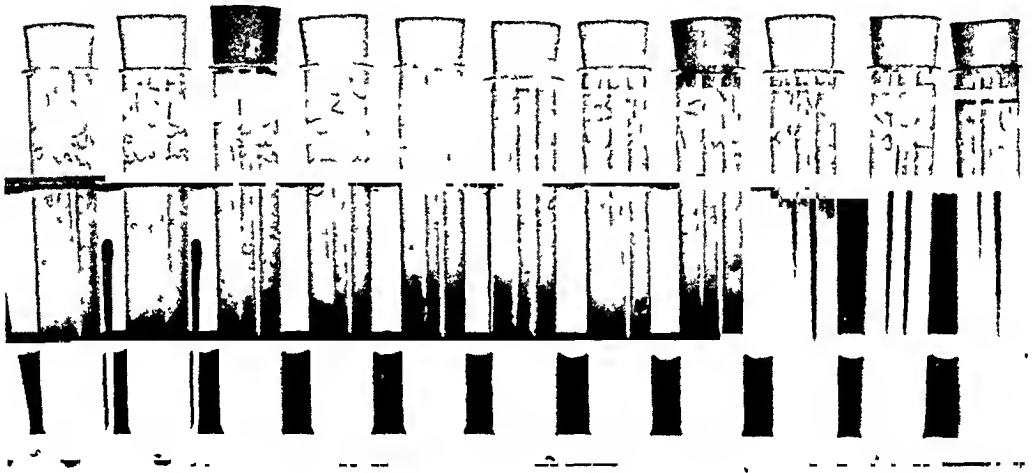


FIG 4—*In vitro* method of testing diffusion of acid through a medium (delivery from a vehicle). Each test tube contains the same amount of methyl cellulose and indicator solution. Above this have been layered different vehicles, each containing the same amount of acid. In the tube on the extreme left the acid has diffused about three-fifths of the way down. The tubes to the right of this show various degrees of diffusion; the two tubes on the extreme right are control tubes without acid. The third tube from the right shows complete lack of diffusion of the acid (from aquaphor).

The treatment would appear to be ideal for small burns where there is no question of shock or ultimate skin grafting. The total healing time is reduced by one-third to one-half, and the possibility of infection is almost entirely eliminated. A soft, pliant, scar is the end-result. The vehicles and acids already proved acceptable by our experiments are convenient enough for use under civilian conditions. The early perfection of the ready and stable powdered material should make use of the acid-débridement method even more acceptable. What is needed now to decide finally on the value of the method is a body of clinical experience.

SUMMARY

The method of débridement with 0.1 molar pyruvic acid in starch paste, first described by Connor and Harvey, was tested on a large group of male

human subjects. The tests were performed by comparing the pyruvic acid-starch paste method with other treatment methods on symmetrically situated small standard third-degree thermal and chemical burns on the flexor aspects of the forearm. (Method of paired comparisons)

The results showed that under the experimental conditions:

(1) Treatment with pyruvic acid-starch paste was more effective than treatment with "blank" starch paste in producing complete and rapid slough removal and, therefore, in accelerating healing.

(2) Treatment with pyruvic acid-starch paste and, subsequent to slough removal, with sodium sulfadiazine cream, produced more rapid healing than: (a) leaving the lesions untreated; or (b) treatment under pressure bandage with 5 per cent sodium sulfadiazine cream; or (c) with 5 per cent sulfadiazine cream; or (d) with $\frac{1}{3}$ per cent silver nitrate in petrolatum.

We believe that our present results also support the concept that the effects of acid débridement are not specific for pyruvic acid. Acid débridement appears to be dependent on the maintenance of the correct supply of hydrogen ions over a sufficient period of time.

Among the other acids tested, 0.1 M. phosphoric acid, which has a p_H of 2.0 and which is a weakly dissociated acid, proved to be the best from all viewpoints. It was approximately as effective in slough removal and in accelerating healing as was 0.1 M. pyruvic acid.

After lengthy studies it was found possible to replace the impractical starch paste vehicle previously used for acid débridement by several other vehicles.

The following formulae were as effective as 0.1 M. pyruvic acid in starch paste vehicle in producing slough removal and in accelerating healing of chemical and thermal burns:

- 0.1 M. pyruvic acid in methyl cellulose—water gel.
- 0.1 M. phosphoric acid in methyl cellulose—water gel.
- 0.1 M. pyruvic acid in methyl cellulose—Sorbitol—water gel.
- 0.4 M. pyruvic acid in K-Y jelly.
- 0.4 M. phosphoric acid in K-Y jelly.
- 0.1 M. pyruvic acid in pectin-glycerin-Ringer's solution gel.

Our final studies, together with Mattocks and Lazier, demonstrated that certain forms of dry hygroscopic powders containing the acids could be prepared. These, on addition of the proper amounts of water, rapidly formed suitable gels. Seven formulae of powders are submitted; these on the addition of water almost immediately formed gels which were shown to be less irritating and almost as effective as pyruvic acid-starch paste in removing slough and promoting healing of chemical and thermal burns.

REFERENCES

- ¹ Glasser, S. T.: A New Treatment for Sloughing Wounds. *Am. J. Surg.*, 50, 32-322, 1940.
- ² Cooper, G. R., Hodge, G. B., and Beard, J. W.: Enzymatic Débridement in the Local Treatment of Burns. *Am. J. Dis. Child.*, 65, 909-911, 1943.

- ³ Howes, E. L.: Progress Report No. 9 Committee on Medical Research of the Office of Scientific Research and Development.
- ⁴ Connor, G., and Harvey, S. C.: The Healing of Deep Thermal Burns. ANNALS OF SURGERY, 120, 362-366, 1944; and personal communication.
- ⁵ Lee, W. E., and Rhoads, J. E.: Present Status of Tannic Acid Method in Treatment of Burns, J. A. M. A., 125, 610-612, July 1, 1944.
- ⁶ Sulzberger, M. B., Baer, R. L., Kanof, A., and Lowenberg, C.: Methods for the Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to the Human Skin. J. Invest. Dermat. 7, 227-238, (Oct.) 1946.
- ⁷ Mattocks, A. M., and Lazier, W. A.: Hydrophilic Acid Ointments for the Débridement of Burns. J. Amer. Pharmac. Assoc., Scientific Edition, 35, 275-279, 1946.

EXTREMITY REFRIGERATION WITHOUT TOURNIQUET LIGATION IN CASES OF ACUTE ARTERIAL DEFICIT*

Lt. (jg) KENNETH E. LIVINGSTON, M.C.,(S), U. S. N. R.

BOSTON, MASSACHUSETTS

FROM THE PERIPHERAL NERVE CENTER, U. S. NAVAL HOSPITAL, OAKLAND, CALIFORNIA.

EXPERIMENTAL STUDIES by Frederick Allen,^{1, 2} in 1938 and 1939, demonstrated that intact limbs can survive complete ischemia for significant periods if adequately cooled. In 1941,^{3, 4} these observations were applied clinically to amputation under tourniquet ligation and refrigeration. There is now considerable clinical experience⁵⁻⁹ to show that this method has real value in preparing for and reducing the risk of amputation in the presence of advancing gangrene and toxic absorption, or in cases of massive trauma to the limb. Absorption from the damaged tissues is terminated by the tourniquet, pain is rapidly alleviated by the cooling, and physiologic amputation is accomplished in the sense that the limb is isolated from the circulation. Anatomic amputation can then be undertaken at reduced risk, and in most instances without supplemental anesthesia.

Limbs which are subsequently to be amputated are ligated by tourniquet and cooled to levels usually 2°-8°C. above freezing. Under these conditions, it has been shown that changes which are probably irreversible occur in the tissues. The tissue changes are a combined result of cooling and of the complete ischemia produced by the tourniquet. On the basis of present clinical experience, tourniquet ligation and refrigeration are appropriate only as preparation for amputation, and cannot safely be employed when survival of the limb is anticipated. However, clinical and experimental studies have not adequately differentiated between pathologic change due to cooling and that secondary to prolonged total ischemia. There is evidence both from clinical and experimental studies that the more severe changes may be attributable to tourniquet ischemia rather than to cooling. It is, therefore, possible that refrigeration *without* tourniquet might be successfully employed in some cases of acute vascular deficit in which survival of the limb is anticipated.

In experimental animals, Bruneau and Heinbecker¹⁰ have found clinical and microscopic evidence of nerve injury after prolonged tourniquet ligation and cooling, but express the opinion that "although direct injury from cold may play a minor rôle, the degenerative changes are regarded as being due essentially to ischemia of the part during and following the cooling period." Evidence that these changes are reversible is apparent in the clinical recovery of the animals, and in the microscopic evidence of reparative processes in the injured nerves. Denny-Brown¹¹ has shown that although loss of myelin and degeneration occur following prolonged cooling, regeneration is rapid and com-

* The opinions expressed in this article are the private views of the author and are not to be construed as official or reflecting the views of the Navy Department.

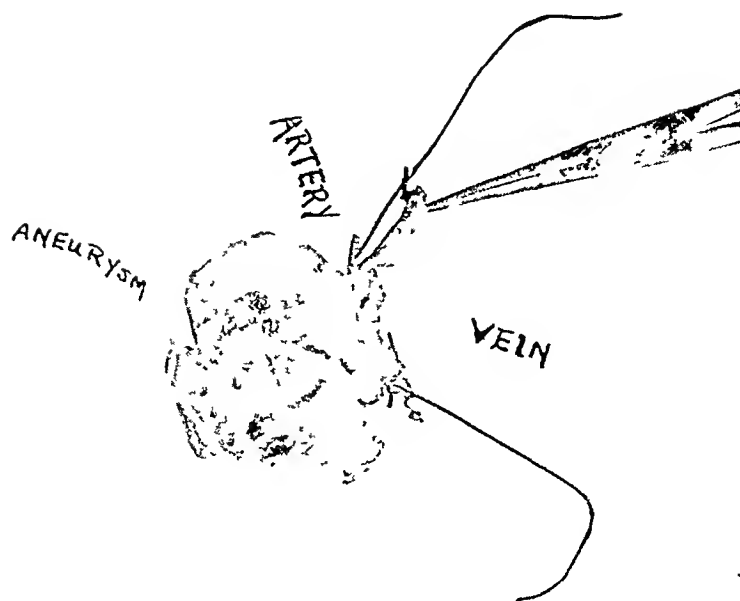


FIG. 1.—Popliteal Aneurysm. The ligature was threaded through the artery to show the opening into the aneurysm. The most recent clot had been removed to show the older thrombus and remaining cavity. There was no arteriovenous communication.



FIG. 2.—Appearance of the foot after four days of cooling. The entire foot was grayish in color, with a dark bluish band about the ankle and heel. This area looked pre-necrotic. There was early drying of the tips of the toes.

plete in all grades of injury short of complete necrosis (produced by hard freezing with carbon dioxide snow).

There are a few clinical reports of refrigeration without the use of tourniquet. In 1944, Ottaway and Foot¹² reported a case in which prolonged refrigeration without tourniquet was used in attempt to preserve an extremity damaged by extensive shell fragment wounds severing the femoral artery and vein. This leg was cooled for one week from 2°–4°C., and then brought slowly up to 14°–16°C. Amputation just above the knee was performed after 29 days of refrigeration. Unfortunately, no pathologic study could be made in this case. Cayford and Pretty,¹³ in 1945, reported a series of 18 amputations under refrigeration in which no tourniquet was used. No pathologic study of the cooled tissues was presented. Richards,¹⁴ in 1944, reported a case in which refrigeration was carried out for a period of 19 days without tourniquet, in an attempt to save a limb following femoral and popliteal embolism. Pathologic studies in this case are of great interest. Muscle showed marked degenerative change "with only sarcolemmal nuclei remaining," the skin showed some epidermal necrosis, and there were "mild degenerative changes" in the nerves. The distal circulation of the leg and foot was remarkably preserved, as shown microscopically and by injection of the vessels. However, conclusions based on this study regarding the value of refrigeration in attempts to save an ischemic extremity were pessimistic. Further clinical experience would be valuable in confirming or modifying these views.

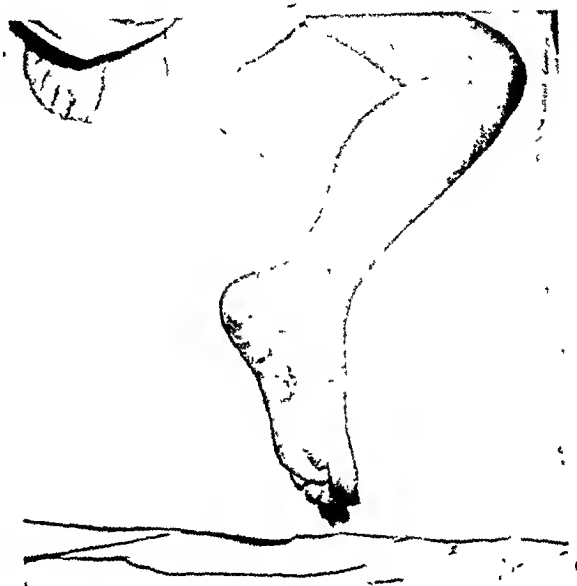


FIG. 3.—Appearance of the foot after 15 days of cooling. The area of marked discoloration about the ankle and heel had cleared, although the upper margin is still discernible. Erythema later developed along this line and finally a fine margin of superficial blistering. The skin and subcutaneous tissues of the weight-bearing areas showed further return toward normal, which persisted until the time of amputation.

We have recently used refrigeration without tourniquet over a period of 30 days in an attempt to save a lower extremity following acute occlusion of the popliteal artery and its major branches. Tissue studies following amputation were of sufficient interest to warrant reporting the case:

Case Report.—This 20-year-old enlisted man was wounded on Okinawa, April 6, 1945, during an enemy strafing attack. He sustained a small shrapnel wound in the left popliteal space at the level of the head of the fibula, with complete loss of peroneal nerve function. Two days after wounding it was noted in his health record that he had "two-plus" edema of the left foot and that "pedal pulses were barely palpable."

He was admitted to this hospital May 23, 1945, six weeks after wounding. Examination showed complete peroneal nerve paralysis with a palpable sensitive proximal neuroma beneath the healed popliteal wound. The foot was hyperesthetic and painful; the leg was

held flexed on the thigh; the foot was dusky and cool and with very poor pulses and slow venous filling after elevation blanching. Beneath the entry wound there was a rounded, walnut-sized pulsating mass with a loud systolic murmur and palpable thrill. With proximal obliteration of the artery there was occasional slowing of the pulse, but no increase in blood pressure. Pedal pulses disappeared completely with compression of the artery proximal to the lesion.

He was placed on a program of intermittent and increasing periods of proximal compression. There was some evidence that his collateral circulation was improving, but, June 18, 1945, there was a sudden arterial occlusion during rest. The foot blanched rapidly and became completely white, the popliteal thrill and pulse disappeared objectively and subjectively, and the foot became rapidly numb and then painful. Within less than one hour from the onset of symptoms he was given spinal anesthesia with a cutaneous level to the xiphoid. There was no change in the color of the foot and no return of pulse. Operation followed immediately, hoping that it would be possible to remove a thrombus from the artery. At operation, there was a large aneurysmal sac (Fig. 1) without associated arterial or venous dilatation. The sac was filled with recent thrombus. The bifurcation of the popliteal was exposed and the artery opened just proximal to this level. There was no clot in either anterior or posterior tibial arteries, but almost no back-bleeding. Quadruple ligation and excision of the shortest possible segment of artery and vein was then carried out. Immediately following operation the foot was unchanged and appeared cadaveric.

It was felt that amputation was inescapable. Refrigeration was undertaken in the hope that if gangrene could be postponed, the collateral bed might be opened sufficiently to allow survival of the foot or permit a more limited amputation (Fig. 2).

It was planned to cool only the distal tissues in which the most severe vascular deficiency existed, in order to avoid setting up spasm of collateral vessels in the calf. It was also planned to cool only to levels that would permit tissue survival and to raise the temperature as rapidly as tolerated. Cooling was started within four hours of the first symptoms of occlusion. Ice bags were used, covering only the foot to the level of the malleoli.

During the first 24 hours the temperature between the toes averaged 16.4°C . It was lowered to 14.3°C . during the next 24 hours, and from that time until cooling was terminated, the temperature ranged between 13.5° to 16.5°C . (56.3° to 61.7°F .) On two occasions on the second and third days the temperature of the foot rose to 20°C ., and in each instance the appearance of the foot definitely changed, cyanosis became more marked and spontaneous pain appeared.

There was little or no pain in the foot while cooling was maintained but there was pain for a period of 10-12 days in the calf. During this period there was marked swelling, amounting to nearly two inches of calf circumference, sufficient to make the skin tight and shiny. This was serious, because we felt that much of his collateral circulation was in the superficial tissues and was probably obstructed by this edema. The edema did not involve the foot, and was undoubtedly due to necrosis occurring in the calf muscle mass. Evidence of this necrosis was still apparent at the time of amputation one month later.

In an attempt to open collateral four spinal anesthetics were given without evident change in the condition of the foot. He received nitroglycerin, in $1/100$ gr. doses, followed later by erythyltetranitrate and intravenous papaverine. It was possible that these medications were helpful, but not to a striking degree.

During the first 10 days it was felt by all observers that amputation was inevitable, but as edema of the calf subsided the foot showed definite improvement. Large areas of blotchy venous stasis which had earlier appeared irreversible cleared completely (Fig. 3). The deep tissues in the weight-bearing areas remained pliable, and skin condition remained excellent until the end of the fourth week. During the fourth week a line of blotchy erythema developed just above the ankle, proximal to the level of cooling. Cooling was then extended proximally to include this area, and during the last few days no attempt

REFRIGERATION WITHOUT TOURNIQUET

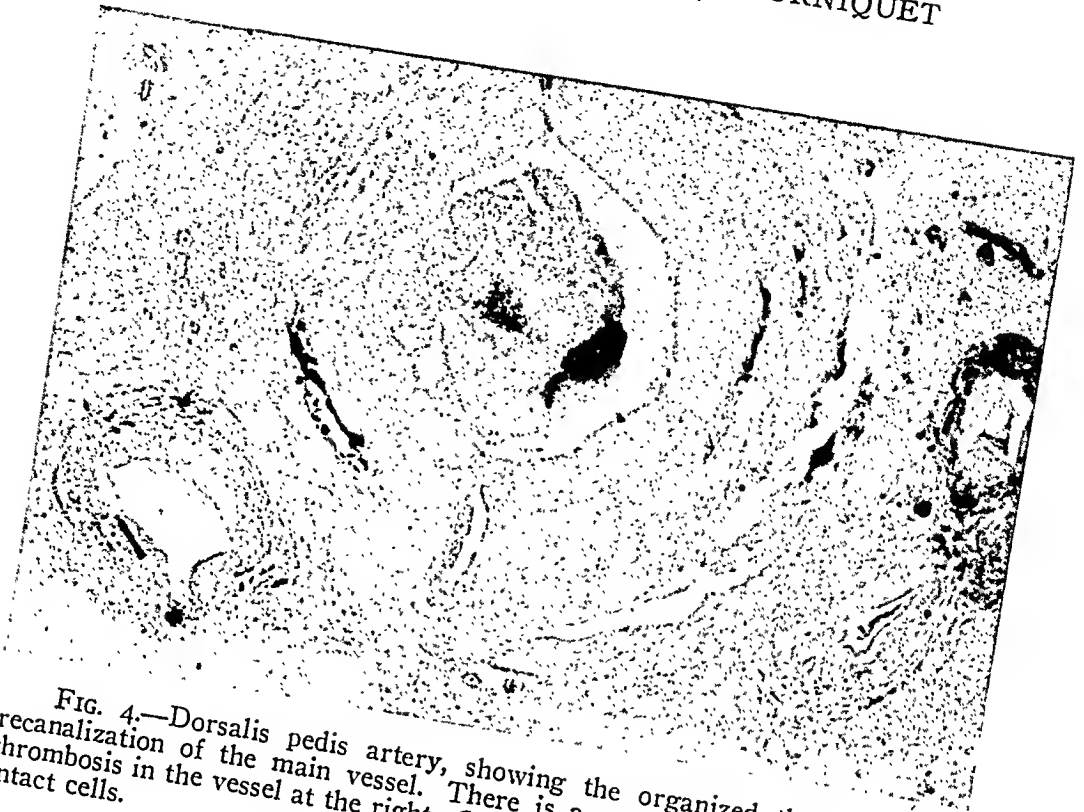


FIG. 4.—Dorsalis pedis artery, showing the organized thrombus with recanalization of the main vessel. There is a small, old, organized mural thrombosis in the vessel at the right. Other vessels were patent and contained intact cells.

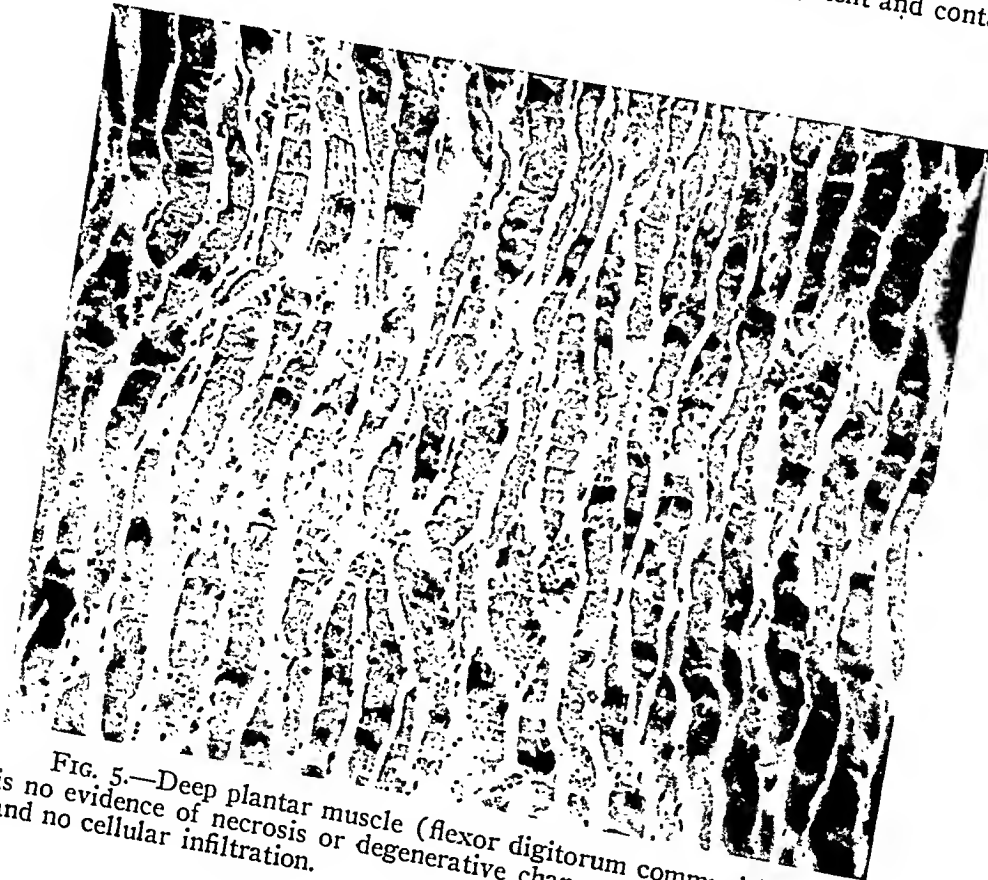


FIG. 5.—Deep plantar muscle (*flexor digitorum communis*). There is no evidence of necrosis or degenerative change in the muscle tissue and no cellular infiltration.

was made to refrigerate the distal portion of the foot. The distal portions of all toes demarcated with dry necrosis. On the 25th day a small line of superficial blistering appeared at the margin of the erythema above the ankle. The remaining areas of the foot looked good, but because this margin of blister persisted he was transferred on the 28th day to an Amputation Center for study. During the following 48 hours cooling was discontinued, and the foot showed considerable deterioration. A marked edema spread over the dorsum of the foot, and superficial blistering developed in this area. On the 30th day amputation was performed six inches below the knee. There was still extensive grayish

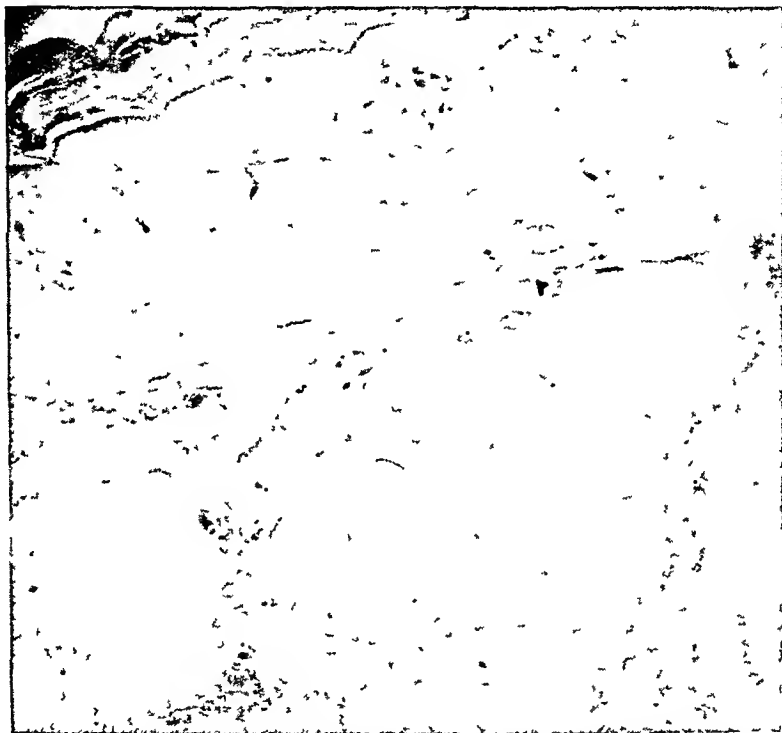


FIG 6—Skin, subcutaneous tissue and fat from plantar surface of the heel. Vessels in all layers appear widely patent and contain intact cells. All weight-bearing areas showed similar microscopic findings.

necrosis of the calf muscle mass and the wound was not closed primarily. Secondary closure later was uncomplicated and the stump was satisfactory.

Pathologic Examination.—*Gross:* Dissection and tissue fixation was done within four hours. Grossly, neither of the major vessels was patent or could be injected for radiopaque roentgenologic studies. Except for the subcutaneous edema over the dorsum of the foot and the superficial blistering in this area, all subcutaneous and deep tissues in the foot looked normal. The skin of all weight-bearing areas was entirely intact, subcutaneous fat was of normal consistency, and muscle tissue appeared normal. *Microscopically,* there was an old organized thrombus in the entire length of the anterior tibial and dorsalis pedis arteries (Fig. 4). These vessels had been extensively recanalized, and the thrombus was well-organized, indicating that it had occurred initially or very soon following the vascular accident. The thrombus in the distal posterior tibial artery was very recent, and probably occurred within the 48-hour period preceding amputation. Beneath one area of marked marginal erythema and blistering above the ankle a microscopic venous thrombosis was found. This occurred in a subcutaneous vein close to denuded skin. The thrombosis contained a large number of polymorphonuclear cells, and was surrounded by a small zone

of perivascular infiltration. This was the only evidence of infection noted in any of the tissues. The process was acute and probably started within the period after cooling was discontinued. No other gross or microscopic thromboses were demonstrable. The distal branches of the peroneal and tibial nerves showed mild degenerative changes.

COMMENT.—In retrospect, we would make certain changes in the management of such a case. First, we would cool the entire limb from the knee distally, in the hope that this would prevent or reduce the marked edema that developed in the calf muscles. It is our opinion that this period of edema interrupted considerable circulation to the distal limb, and was a serious complication. Secondly, we would suggest alcohol block or lumbar sympathetic ganglionectomy on the affected side. Although there was no definite evidence from spinal anesthetics that vasospasm was a significant factor in this case, sympathetic interruption would have assured maximal delivery of blood to the deficient area.

SUMMARY

Following an acute and severe vascular accident secondary to traumatic aneurysm of the popliteal artery, cooling of the distal extremity was carried out for a period of 28 days prior to amputation. During the interval of observation, changes which were assumed by all observers to have been irreversible regressed, and the appearance of the foot strikingly improved. Following amputation there was gross and microscopic evidence that revascularization was taking place in the cooled tissues and that the nutrition of the deep muscle tissues and weight-bearing skin and subcutaneous tissue of the foot had been well-maintained. These studies did not indicate that the smaller circulation in the cooled areas had been extensively shut down by vasoconstriction due to cold. On the contrary, we were impressed by the wealth of small patent vessels in all tissues and also by the active recanalization processes in the thrombosed segments of major arteries.

BIBLIOGRAPHY

- ¹ Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs. *Am. J. Surg.*, 45, 459-465, 1939.
- ² Allen, F. M.: Experiments Concerning the Ligation and Refrigeration: With Respect to Local Intoxication and Infection. *Surg., Gynec. and Obst.*, 68, 1047-1051, 1939.
- ³ Allen, F. M.: Reduced Temperatures in Surgery. *Am. J. Surg.*, 52, 225-237, 1941.
- ⁴ Crossman, L. W., Ruggiero, W., Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery. *Arch. of Surg.*, 44, 139-156, 1942.
- ⁵ Perlow, S.: Refrigeration Anesthesia in Leg Amputation. *U. S. Naval Med. Bull.*, 42, 433-437, February, 1944.
- ⁶ Hinchey, P. R.: Refrigeration in Surgery of the Extremities. *N. E. J. M.*, 230, 63-69, January 20, 1944.
- ⁷ O'Neil, E. E.: The Use of Refrigeration in Amputations and Peripheral Vascular Disease. *N. E. J. M.*, 230, 209-216, February 24, 1944.
- ⁸ McElvenny, R. T.: Refrigeration in Trauma of the Extremities. *Surg. Clin. of N. America*, 25, 192-209, February, 1945.

- ⁹ Mock, H. E.: Refrigeration in Trauma: Clinical Report. *Am. J. Surg.*, **67**, 424-435, February, 1945.
- ¹⁰ Large, A., and Heinbecker, P.: Nerve Degeneration following Prolonged Cooling of Extremities. *ANNALS OF SURGERY*, **120**, 742-749, November, 1944.
- ¹¹ Denny-Brown, D.; Adams, Raymond D.; Brenner, Charles, and Doherty, Margaret M.: The Pathology of Injury to Nerve Induced by Cold. *J. Neuropath. & Exp. Neurol.*, **4**, 305-323, October, 1945.
- ¹² Ottaway, J. P., and Foote, J. J.: Refrigeration of Wounded Extremities. *U. S. Naval Med. Bull.*, **43**, 1041-1043, November, 1944.
- ¹³ Cayford, E. H., and Pretty, G.: Refrigeration Anesthesia and Evaluation of Amputation Sites by Arterogram. *ANNALS OF SURGERY*, **121**, 157-163, February, 1945.
- ¹⁴ Richards, V.: Refrigeration Anesthesia in Surgery. *ANNALS OF SURGERY*, **119**, 178-200, February, 1944.

PRIMARY FIBROSARCOMA OF THE LIVER*

THOMAS A. SHALLOW, M.D., AND FREDERICK B. WAGNER, JR., M.D.

PHILADELPHIA, PA.

FROM THE SAMUEL D. GROSS SURGICAL DIVISION OF THE JEFFERSON MEDICAL COLLEGE HOSPITAL

THE ABDOMINAL SURGEON may at any time be confronted with a primary hepatic tumor requiring resection. Numerous reports, dating back many years, have proven the feasibility of this seemingly formidable procedure. Cures for as long as seven years following removal of malignant tumors¹ have dispelled doubt as to its value. So few cases are encountered by the individual surgeon, however, that his knowledge of the most suitable methods of excision for particular types is dependent upon the isolated experience of others. It is the purpose of this paper to add an unusual case of primary fibrosarcoma of the liver and to review the accepted methods of resection.

Case Report.—A. V., a white male, age 60, was admitted as a private patient to the Jefferson Medical College Hospital, November 18, 1945, with the chief complaint of abdominal enlargement.

The patient was well until July, 1945, at which time he began to experience a persistent bitter taste in his mouth. In August he observed an enlargement of his abdomen. At this time he began to lose his appetite. After eating only a small fraction of his normal meal, he would feel distended and extremely uncomfortable. During the ensuing three and one-half months before admission the abdominal enlargement gradually increased, he lost 40 pounds in weight, and grew progressively weaker.

The past medical and family histories were not significant.

Physical Examination.—The patient was a somewhat emaciated elderly male who appeared chronically ill. There was slight paleness of the mucous membranes but no evidence of jaundice. The temperature was 99.4° F.; pulse 100; respirations 24; and blood pressure 150/90. The significant findings locally were confined to the abdomen. On inspection, there was a dome-shaped enlargement resembling that seen in pregnancy at full term, the greatest prominence, however, appearing to be upper abdominal. Palpation revealed a round, firm, smooth, nontender mass about ten inches in diameter, fixed in the upper abdomen but somewhat movable below. It descended with respiration and was dull to percussion. A fluid wave could not be elicited.

Laboratory Studies.—The hemoglobin was 68 per cent; red blood cells 3,400,000, and white blood cells 8,500 per cu. mm., the differential count revealing 73 per cent neutrophils (3 per cent young forms), 21 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. Routine urinalyses and Fishberg concentration test were normal. A plain roentgenogram of the chest was negative. Roentgenologic study of the gastro-intestinal tract with barium revealed upward and backward displacement of the stomach and small bowel by a soft-tissue mass lying anteriorly. The six-hour film showed the stomach and small bowel still displaced in ringlet-formation around the mass (Fig. 1a). The colon was displaced anteriorly and to the periphery of the mass (Fig. 1b). There was no evidence of peptic ulcer or intrinsic gastro-intestinal neoplasm. These findings were interpreted as probably due to an omental cyst.

Preoperative Course.—A high caloric, high protein, high carbohydrate, low fat diet, and large doses of vitamin K were administered. During the eight days prior to operation

* Read before the Philadelphia Academy of Surgery, April 8, 1946.

the temperature fluctuated between normal and 100° F., and the pulse between 80 and 100. *Preoperative Diagnosis:* Possible omental or mesenteric tumor.

Operation.—November 26, 1945: Under pontocaine spinal anesthesia, a right rectus muscle-splitting incision was made over the summit of the mass and the peritoneal cavity entered. No free fluid was encountered. A firm, highly vascular, peritonized tumor was exposed, replacing most of the left lobe of the liver and extending downward to the level of the iliac crests. It was slightly adherent by fine adhesions to the surrounding coils of bowel.



FIG. 1.—Gastro-intestinal series, showing stomach and small bowel in (a) and colon in (b) displaced in ringlet-formation around the mass.

An attempt was made to free the mass from the under surface of the liver, but considerable hemorrhage was encountered, and this method of approach had to be abandoned. The mass itself as well as the left lobe and part of the right lobe of the liver were then delivered into the incision. It was now found that the blood supply to the tumor could be controlled by an approach from its posterior aspect. Numerous large vessels, many the size of the radial artery, were encountered. Each was divided as it was exposed. When about half of the tumor was freed by this method, the entire tumor and remainder of the left lobe could then be delivered easily and completely into the incision. The remainder of the blood supply to the tumor was exposed and clamped as the tumor and immediately adjacent portion of left lobe were removed. Part of the round ligament was involved by the tumor and was included in its removal.

At the completion of resection, about one-third of the left lobe remained, and was a thin shell which oozed blood and bile. Suture ligatures were applied to the large vessels controlled by the clamps. The oozing was controlled by approximating the two raw areas of the under surface of the liver with interrupted mattress sutures of No. 2 chromic catgut. An iodoform gauze pack was placed against the sutured liver bed and a Penrose drain adjacent to the foramen of Winslow. The wound was then closed in layers around the drains.

The patient received 500 cc. of whole citrated blood during the operation, which lasted 55 minutes, and he remained in good condition.

FIBROSARCOMA OF LIVER

Pathologic Examination.—*Gross:* The specimen consists of a peritonized nodular mass of tissue weighing 5,200 Gm. (Fig. 2). On cut-section there are a few areas, but for the most part the tissue is firm and smooth. *Histologic Examination.*—The section consists of tissue from a tumor attached to the liver. It is made up of bundles of fibrous tissue that, in general, do not show much change (Fig. 4). Sections taken from the central portion of the tumor,

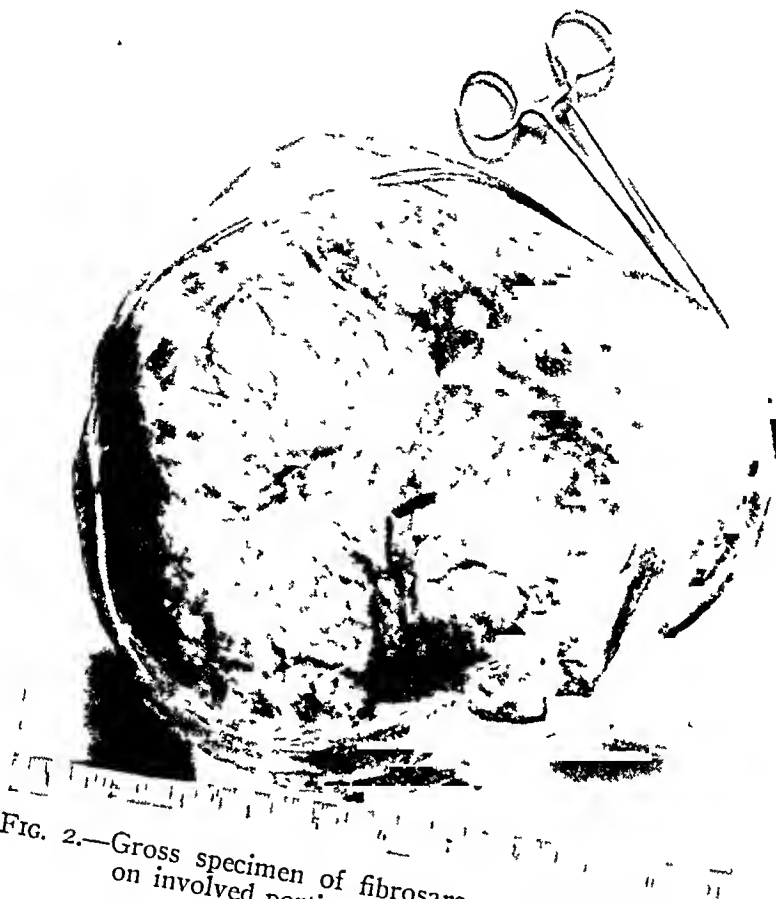


FIG. 2.—Gross specimen of fibrosarcoma, with hemostat on involved portion of round ligament.

however, are very cellular and show very definite sarcomatous change (Fig. 5). There are many large giant cells and many cells with multiple nuclei. Throughout the tumor there is extensive necrosis. *Pathologic Diagnosis:* Fibrosarcoma of the liver. *Postoperative Course.*—The immediate postoperative response and early convalescence were uneventful. Small quantities of bile drained from the wound for three days. The drains were gradually withdrawn between the 7th and 10th postoperative days, during which time the patient tolerated a full house diet and was apparently doing well. The vital readings remained essentially normal after the 4th postoperative day. On the morning of the 11th day he got out of bed unaided and collapsed. In spite of artificial respiration and administration of cardiorespiratory stimulants, the patient promptly expired. Permission for postmortem examination could not be obtained. The cause of death was thought most probably due to embolism.

DISCUSSION.—The vast majority of primary hepatic tumors are epithelial, originating in liver cells (benign and malignant hepatomas) or in bile ducts (benign and malignant cholangiomas). Carcinoma of the liver cells is the most common. Warvi² collected 1,200 histologically-studied cases up to 1944. The



FIG. 3.—Cut-section of tumor, showing central sarcomatous area.

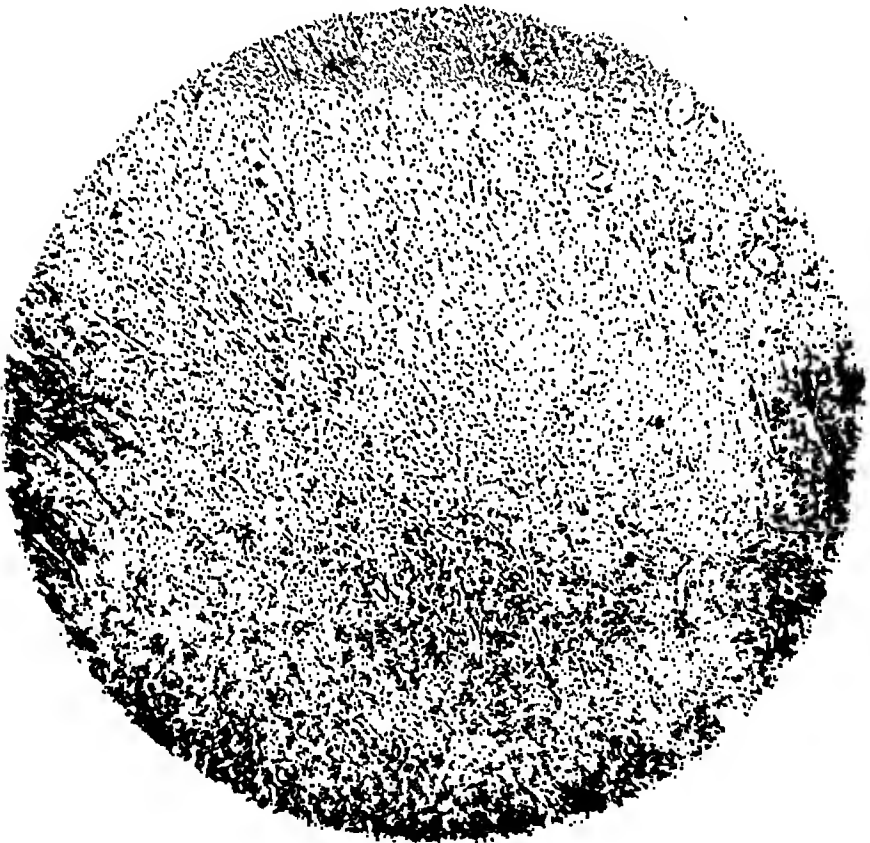


FIG. 4.—Photomicrograph of tissue from periphery of tumor, showing whorls of fibrous tissue with apparently benign appearance. ($\times 75$)

percentage of carcinomas of the liver that are primary is stated by Jaffe³ as 1.5 to 3.0.

The mesenchymal tumors are far less common, originating in nonspecific elements of the liver, vascular or stromal. Tumors of vascular origin, particularly hemangiomas comprise the greater part. An accurate count of the reported cases of primary sarcoma is almost impossible because of the confusion in classification, the histologic similarity between highly anaplastic carcinoma and

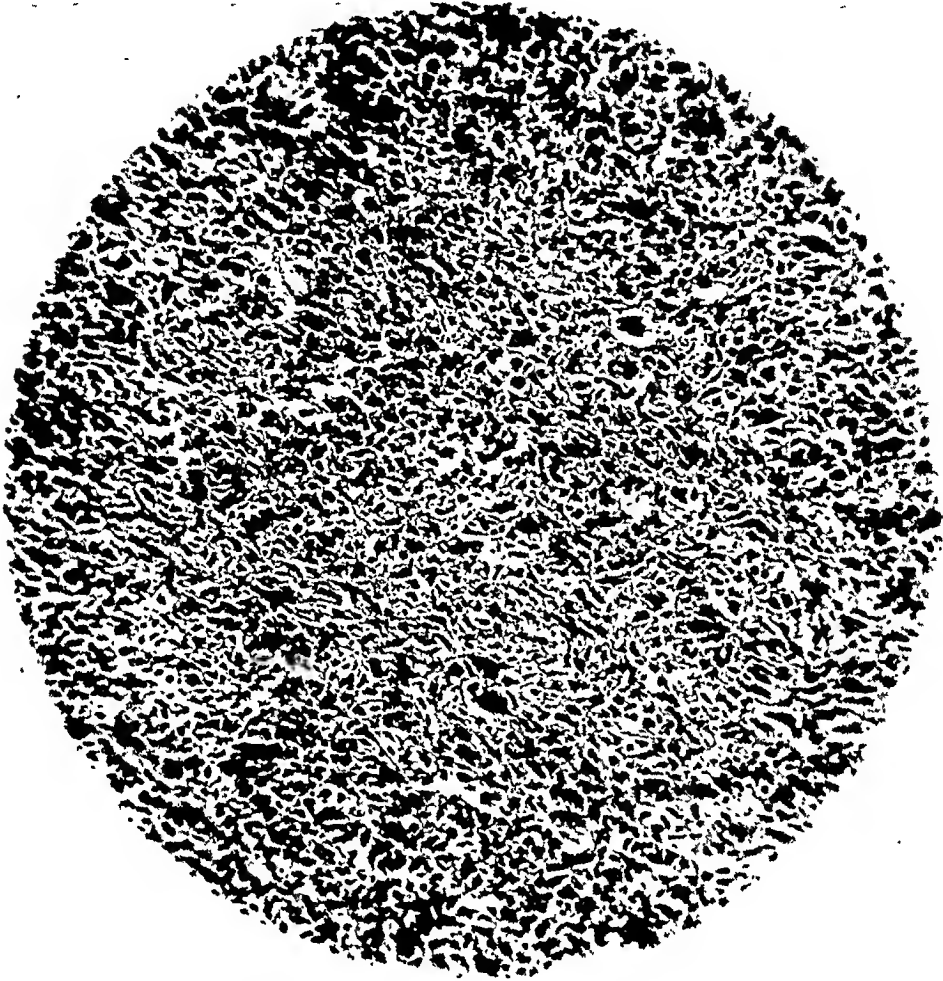


FIG. 5.—Photomicrograph of tissue from sarcomatous central area of tumor, showing extreme cellularity, hyperchromatism of nuclei, and multi-nucleated cells. (x 200)

sarcoma, and the difficulty in some instances of ruling out origin of the tumor from the diaphragm or thoracic wall. Thus, Jaffe,³ who reviewed the literature in 1924, collected 48 cases, while Goldstein,⁴ in the same year, collected 59. Miller⁵ collected 30 additional cases for his review in 1939. It is probable that the total number of histologically-studied cases of primary sarcoma is not more than 100 at the present time.

Ewing⁶ states that the true source of primary hepatic sarcomas has never been actually traced, although various opinions have been voiced in the literature. These have included origin from the connective tissue about the blood vessels or acini (Arnold⁷); the cellular elements of the vessels (Delepine⁸);

the perilymphatic connective tissue (Byrom⁹); the normal connective tissue (Demel¹⁰); the new connective tissue in portal cirrhosis (29 per cent of cases were associated with cirrhosis according to Jaffe³) or syphilitic cirrhosis (Hedren¹¹); the wall of a chronic abscess (Goldstein¹²); the wall of an echinococcus cyst (De Vecchi¹³); or a preëxisting cavernoma (Marx¹⁴). Dubs¹⁵ reported a case of spindle cell sarcoma in a 26-year-old girl who died six months after an injury to the liver. In the authors' case the tumor may have arisen from the connective tissue of the round ligament.

Fibrosarcomas of the liver do not differ pathologically from those found elsewhere in the body. According to Jaffe,³ they are not prone to produce metastases.

The symptoms and signs of malignant tumors of the liver are subject to wide variation. The patient may be asymptomatic; there may be a history merely of an upper abdominal mass; other patients, usually those with late lesions, may show evidence of cirrhosis, jaundice, ascites, and cachexia. Jaundice depends upon the location of the tumor with respect to the large biliary ducts. Pain in the lumbar, flank, epigastric, or shoulder regions is usually a late symptom and has been attributed to distention of the capsule.

Only after thorough clinical and laboratory studies have failed to disclose a primary tumor elsewhere, should the possibility of primary hepatic tumor be considered. Certain preoperative differentiation between carcinomatous and sarcomatous lesions is not possible unless peritoneoscopy, with biopsy of the tumor mass for microscopic study, is performed. As in the authors' case, the diagnosis of primary hepatic sarcoma is usually not thought of, let alone actually made.

The treatment of primary tumors of the liver is surgical resection. According to Warvi,² normal and neoplastic liver tissue are both highly radioresistant, and the severe systemic reactions resulting from irradiation of the upper abdomen contraindicate roentgenotherapy. On the other hand, if the general condition of the patient is poor; if distant metastasis or regional lymph node metastasis at the liver hilum can be demonstrated; if the growth involves the major bile ducts and blood vessels at the hilum; if the remaining area of liver appears involved or if marked reduction of hepatic function indicative of extreme parenchymal involvement exists, then resection likewise is contraindicated.

The anesthetic should provide good relaxation, be nontoxic to the liver, and permit maximal oxygenation of the blood. For this purpose spinal or cyclopropane anesthesia are suitable.

Adequate exposure for resection may be obtained by either a transverse or transrectus incision. Exposure may be further facilitated by hyperextension of the spine, severance of the falciform or triangular ligaments, and insertion of an inflated rubber glove to keep the liver down from the diaphragm.

The various methods of hepatic resection merely represent different ways of dealing with the major technical problem of control of hemorrhage. An incision which radiates out from the liver hilum will reduce the number of severed vessels and ducts, and thereby reduce hemorrhage. Undue hemorrhage

can be controlled temporarily by manual pressure on the aorta above the celiac axis. The hepatic artery may be compressed within the hepatoduodenal ligament by finger pressure or by a rubber padded clamp. This procedure, if employed for more than ten minutes, is apt to be followed by a profound fall in blood pressure. It may be employed for a few minutes as a life-saving procedure in the face of violent uncontrollable hemorrhage, but, as emphasized by Tinker,¹⁶ is undesirable as a routine. As an aid in the control of moderate hemorrhage, Warvi¹⁷ has summarized the following measures: digital compression of the cut liver edge; tourniquet of the liver proximal to the bleeding edge; tamponade of the bleeding surfaces; application of spring clamps or rubber-shod intestinal clamps near the edge; or controlling the oozing with adrenalin solution 1:1000, making the larger bleeding vessels discernible enough to be clamped and ligated. To these measures may be added the use of thrombin, topically applied as a powder or solution. Although to date there are no reports of the use of thrombin in humans to control bleeding in hepatic resection, animal experiments indicate that this substance may be of great aid in operations upon the liver. Tidrick, and coworkers,¹⁸ report its successful use in the control of persistent oozing from the gallbladder bed of the liver following cholecystectomy.

Early attempts at removal of hepatic tumors were made by employing elastic ligature compression of the tumor stump, usually with extraperitonization of the stump (Cousins,¹⁹ 1874). The tumor was then cut distal to the ligature, or else allowed to slough off. Another early method (Clementi,²⁰ 1890) featured the application of one or more clamps at the tumor base which were left in place. In some instances the entire clamps were exteriorized (Lapoint,²¹ 1897), while in others only the handles were exteriorized through a stab incision (Kocher,²² 1902).

In the actual resection of liver tissue not only has the scalpel been used, but also simple cautery (Escher,²³ 1886) and electrocautery (McLean,²⁴ 1929). Suturing of the liver with a blunt needle for hemostasis just proximal to the contemplated line of resection has been advocated (Kousnetzoff and Pensky,²⁵ 1896). Raw surfaces should preferably be approximately directly, as in the authors' case, but, when this is not entirely feasible, omentum or gauze packing may be sutured in between.

According to Pickrell and Clay,²⁶ when the tumor occurs in the left lobe of the liver, it is preferable to do a complete lobectomy rather than a local removal of the tumor. These authors cut the falciform ligament close to its diaphragmatic attachment to aid in exposure and delivery, apply hemostatic sutures at the division between right and left lobes, resect the left lobe, and reperitonize the raw area with the flap of falciform ligament. They claim the advantages of wider resection of the lesion without embarrassment of hepatic function, decreased bleeding, and complete peritonization of raw areas.

The most important general postoperative complications following this type of surgery are metabolic, consisting early of "liver shock" or hepatorenal syndrome and later of malnutrition. These may be prevented in most instances by proper dietary management. Locally, sinuses draining bile, necrotic slough,

or pus may persist in the wound for varying lengths of time. According to Warvi,¹⁷ secondary hemorrhage has occurred in only 2 per cent of cases of hepatic resection since the beginning of the century. Postoperative ileus, atelectasis and pneumonitis may occur, as in other upper abdominal operations. The incidence of pulmonary embolism is not outstanding following hepatic resection. Its unfortunate occurrence in the authors' case is regarded as one which might have followed any upper abdominal operation for cancer in an elderly patient.

SUMMARY AND CONCLUSIONS

1. A case of primary fibrosarcoma of the liver, in which the lesion weighed 5,200 Gm., is reported in detail. The patient died suddenly on the 11th postoperative day, probably of pulmonary embolism.

2. The various methods of resection of hepatic tumors are discussed. A knowledge of these is essential in order to deal successfully with the unusual technical problems which these tumors may present.

REFERENCES

- ¹ Yeomans, F. C.: Primary Carcinoma of the Liver. *J. A. M. A.*, 64, 1301, 1915.
- ² Warvi, W. N.: Primary Neoplasms of the Liver. *Arch. Path.*, 37, 367, 1944.
- ³ Jaffe, R. H.: Sarcoma and Carcinoma of the Liver following Cirrhosis. *Arch. Int. Med.*, 33, 330, 1924.
- ⁴ Goldstein, H. I.: Primary Malignant Tumors of the Liver. *M. J. and Rec.*, 120, 120, 1924.
- ⁵ Miller, J. K.: Primary Sarcoma; Endothelioblastoma; Case Report. *Am. J. Surg.*, 44, 458, 1939.
- ⁶ Ewing, J.: Neoplastic Diseases. Fourth Ed., Philadelphia. W. B. Saunders Co., 1940, p. 752.
- ⁷ Arnold: Ziegler's Beiträge z. path. Anat., 8, 123, 1890; quoted by Ewing.⁶
- ⁸ Delepine: Trans. London Path. Soc., 42, 161, 1891; quoted by Ewing.⁶
- ⁹ Byrom: Quoted by De Vecchi¹³ and by Ewing.⁶
- ¹⁰ Demel: Z. p. i. sc. med., Torino, 24, 273, 1900; quoted by Ewing.⁶
- ¹¹ Hedren: Quoted by Saltykow: Sarcoma and Carcinoma of the Liver. *Cor. Bl. f. schewiz. Aerzte*, 44, 385, 1914; quoted by Jaffe.³
- ¹² Goldstein: *Internat. Clin.*, 2, 73, 1921; quoted by Jaffe.³
- ¹³ De Vecchi: *Soc. Med. Chir. de Bologna* 6, June, 1908; quoted by Jaffe.³
- ¹⁴ Marx, H.: *Centralbl. f. allg. Path.*, 15, 433, 1904; quoted by Ewing.⁶
- ¹⁵ Dubs: *Deutsch. Ztschr. f. Chir.*, 138, 1, 1917; quoted by Jaffe.³
- ¹⁶ Tinker, M. B. and Tinker, M. B., Jr.: Resection of Liver: Conditions Favorable for Operation; Methods; Experimental Studies. *J. A. M. A.*, 112, 2006, 1939.
- ¹⁷ Warvi, W. N.: Primary Tumors of the Liver. *Surg., Gynec. and Obst.*, 80, 643, 1945.
- ¹⁸ Tidrick, R. T., Seegers, W. H., and Warner, E. D.: Clinical Experience with Thrombin as a Hemostatic Agent. *Surgery*, 14, 191, 1943.
- ¹⁹ Cousins: Quoted by Warvi.¹⁷
- ²⁰ Clementi: Quoted by Warvi.¹⁷
- ²¹ Lapoint: *Le Bull. Med.*, 1897, p. 883; quoted by Warvi.¹⁷
- ²² Kocher: Quoted by Warvi.¹⁷
- ²³ Escher: Quoted by Warvi.¹⁷
- ²⁴ McLean, A. J.: Bovie Electrosurgical Current Generator: Some Underlying Principles and Results. *Arch. Surg.*, 18, 1863, 1929.
- ²⁵ Kousnetzoff and Pensky: Quoted by Warvi.¹⁷
- ²⁶ Pickrell, K. L., and Clay, R. C.: Lobectomy of the Liver. *Arch. Surg.*, 48, 267, 1944.

SIMULTANEOUS REPAIR OF PERIPHERAL NERVE AND SOFT TISSUE DEFECTS IN THE FOREARM

MAJOR FRANK F. ALLBRITTEN, JR.

MEDICAL CORPS, ARMY OF THE UNITED STATES

EARLY INITIAL SURGERY, blood replacement therapy, bacteriostatic drugs, and reparative surgery have been responsible for preserving many seriously injured extremities in World War II. Often these extremities have suffered extensive soft tissue loss and have presented problems in reconstructive surgery. Soft tissue defects healed with extensive cicatrix and covered by split-skin grafts are neither sightly nor functionally adequate. Underlying tendons and muscles are often adherent and their function is impaired. Concomitant bone and nerve injuries are usual and attempts at repair made through scar tissue often end in failure (Fig. 1, A and B). Therefore, it has become an accepted measure to excise all scar tissue from the extremity and to fill the defect with a graft of more normal fat and skin before considering additional reconstructive efforts.

Several weeks may be required to cover the soft tissue defects in the forearm by use of a tubed graft. A "pattern" or "flap" graft from the abdominal wall can usually be completed in a period of one month. However, before the wound can be opened again for reconstructive procedures several additional weeks elapse while the blood supply to the transplanted tissues becomes established.

It was thought that if the soft tissue defect could be corrected and the injured nerve repaired at a single operative procedure the time of hospitalization of the patient could be shortened considerably. Certain other advantages would be offered by such a procedure. The early replacement of an encircling, binding, cicatrix of the forearm by more normal tissue would greatly improve the nutrition of the hand, edema would be lessened, the soft tissues would become more supple. Release of scar tissue adhesions would aid in early restoration of full extent of joint movement and permit useful function of the extremity to be resumed. In addition to these considerations the time factor influencing nerve regeneration must be taken into account. Nerve repair soon after injury offers optimum conditions for regeneration. The prolonged delay in nerve repair that is so common in extensive soft tissue injuries results in increased fibrosis in the distal nerve segment and atrophy of muscle tissue that ultimately is manifest by impaired or complete failure of return of function.

Patients with extensive soft tissue defects in an extremity often have extensive loss of nerve substance. Approximation of unscarred nerve ends without tension then requires an extensive mobilization of the nerve. In the arm, forearm, and wrist the defect is usually overcome by transplant of the nerve across a joint in flexion. Total time of immobilization of the joint can be reduced appreciably if the healing of the soft tissue defect and the site of nerve suture can occur simultaneously.

In consideration of these possibilities the following plan of treatment has been used. The first stage consists of the following: (1) The scar tissue is meticulously excised; (2) the nerve is explored, mobilized, transplanted and sutured (Fig. 1C); (3) a pattern flap is raised from the abdomen to cover the

FIG. 1A

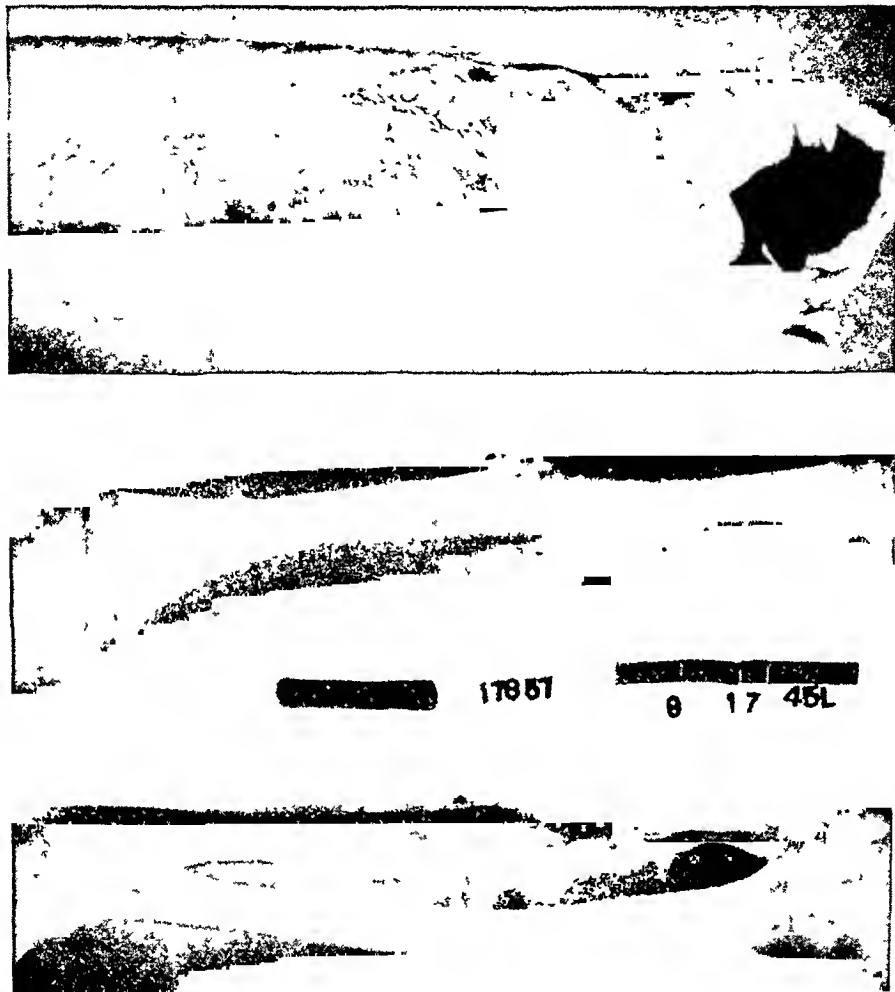


FIG. 1B

FIG. 1A and B.—The large soft tissue defect and bone destruction resulting from a rifle bullet wound of the forearm. Complete paralysis of ulnar nerve. Split-thickness skin graft had been applied during early reparative surgery.

soft tissue defect; (4) the skin and subcutaneous tissue of the abdominal wall is mobilized about the site from which the flap was raised and is closed by retention sutures (Fig. 1D); (5) the raised pattern flap is sutured to the defect in the forearm over a broad area and opposing margins of the abdominal

REPAIR OF DEFECTS IN FOREARM

and forearm wounds are carefully approximated in order to completely close the wound (Fig. 1E); and (6) the forearm is immobilized in a suitable position with an adhesive dressing and the joints of the wrist and the hand are free for active movements. The skin sutures may be removed in seven days and the retention sutures removed in fourteen days. At the end of this

FIG. 1C

FIG. 1E



FIG. 1D

FIG. 1F

FIG. 1C.—All scar tissue has been excised. The ulnar nerve has been transplanted anterior to the elbow joint and a defect of 10 centimeters in the continuity of the nerve closed by suture of the nerve ends.

FIG. 1D.—The abdominal flap cut to the pattern of the defect is raised. The edges of the abdominal wound have been widely mobilized and approximated with retention sutures.

FIG. 1E.—The flap graft is sutured into position. The opposite edge of the defect in the forearm is sutured to the adjacent edge of the abdominal wound to accomplish a completely closed wound.

FIG. 1F.—Soft tissue defect closed and nerve repaired six weeks after beginning of operative procedure.

period the wound should be firmly healed. It has been customary to use penicillin prophylactically during this period.

The second stage is undertaken in three or four weeks. It consists of the following parts: (1) Division of the pedicle flap at its site of attachment to the abdomen; (2) suture of the abdominal wound; and (3) suture of flap to edge of defect in the forearm. Skin sutures can be removed in seven days and

FIG. 2



FIG 3

FIG. 2.—End-result of combined repair of median nerve and soft tissue defect. Total time of five weeks from beginning of procedure until all sutures were removed. Subsequent examinations have shown normal progress of nerve regeneration.

FIG. 3.—End-result in patient with combined ulnar nerve suture and repair of soft tissue defect at wrist. A previous attempt at nerve suture through the cicatricial tissue had failed for the operative wound disrupted. Total time of six weeks from the beginning of the procedure to its completion. Follow-up examinations have shown usual progress in nerve regeneration.

the movement of all joints started (Fig. 1F). Penicillin has been given prophylactically until the wound has healed.

The use of this method has produced satisfactory results from the aspect of nerve regeneration and repair of the soft tissue defects. The accompanying illustrations and legends give representative cases.

SUMMARY

Nerve repair combined with pattern flap grafts to soft tissue defects in the forearm is described.

The advantages of this procedure are: (1) A decrease in the period of hospitalization; (2) an early nerve repair; and (3) a decrease in the time of immobilization of the joints of hand and elbow.

REFERENCES

- Brown, J. B., Cannon, B., Graham, W. C., Lischer, C. E., Scarborough, C. P., Davis, W. B., and Moore, A. M.: Direct Flap Repair of Defects of the Arm and Hand. *ANNALS OF SURGERY*, 122, 706-715, October, 1945.
- Bunnell, S.: *Surgery of the Hand*. Philadelphia, J. B. Lippincott Company, 1944.
- Higbet, W. B., and Saunders, F. K.: Effects of Stretching Nerves after Suture. *Brit. J. Surg.*, 30: 355-369, April, 1943.
- Holmes, W., and Young, J. Z.: Nerve Regeneration after Immediate and Delayed Suture. *J. Anat.*, 77, 63-96; 1942.
- Subcommittee on Neurosurgery, Division of Medical Sciences of the National Research Council: *Neurosurgery and Thoracic Surgery*. Philadelphia, W. B. Saunders Company, 1943.

BACTERIOLOGIC STUDY OF BURN WOUNDS*

A COMPARISON OF THE BACTERIAL FLORA OF BURN WOUNDS OF PATIENTS
TREATED WITH SULFONAMIDES OR PENICILLIN

JOHN L. LANGOHR, M.D., CORA R. OWEN, PH.D., AND OLIVER COPE, M.D.

BOSTON, MASSACHUSETTS

FROM THE DEPARTMENT OF SURGERY OF THE HARVARD MEDICAL SCHOOL AND THE SURGICAL SERVICES
AT THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS

PART I

AS LONG AS the contaminating bacteria of a burn wound are able to flourish, the resulting infection will be *the* deterrent to the healing of the wound. These bacteria do not flourish in a shallow, partial-thickness wound and, therefore, infection and retarded healing are not to be countenanced. It is suspected that this shallow wound does not nourish them. Prompt healing, therefore, is anticipated and the claims for various methods for expediting healing of the partial-thickness burn wound are discounted. In a full-thickness burn wound the bacteria flourish and will unless something is done to starve, kill or remove them.

To do one or more of these has been attempted by many methods, both local and systemic, and none has been entirely successful. Agents in the form of solvents, such as Dakin's solution, corrosive and coagulating chemicals and the more selective vital dyes have been applied to the wound surface; judged to discourage the bacterial growth and the infectious process, in their toxicity they have proved damaging to viable cells. The sulfonamides applied locally do not damage viable cells but, limited to an antistreptococcal specificity, they have failed to block the generation in the wound of other bacterial species equally insidious. Every effort to control the less susceptible organisms by increasing the local concentration of a sulfonamide drug is thwarted by its rapid absorption from the wound and a rise in concentration to toxic levels of the drug in the body fluids and renal shut-down. So predictable is this absorption that only in burns of minor extent can sulfonamides be applied in a medium permitting high and broadly useful concentrations.† The drug,

* The work described in these papers was done under a contract, recommended by the committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

† The possibility that the rapid absorption of sulfonamides from burn wounds might result in toxic levels of the drug in the extracellular fluid was reported in 1941 by Hooker and Lam.¹ Renal shut-down, with sulfonamide poisoning, was observed in two patients treated at the Massachusetts General Hospital in 1942. An extensively burned patient whose wounds were sprayed with triethanolamine containing 3 per cent sulfadiazine (Pickrell's solution²) developed a blood level of 37 and 54 mg./100 cc. of sulfadiazine on the 3rd and 5th days after injury and the initial application. Complete urinary suppression occurred on the 2nd day, and was unrelieved. Death in uremia occurred on the 6th day. Sulfanilamide powder applied to a large full-thickness wound of the second patient (Case 76) on the 11th day after injury was followed 24 hours later by a blood level of 21 mg./100 cc. Renal damage contributed to the death on the 27th day. The failure of sulfonamides in certain ointments to rise to toxic levels in the body fluids^{3, 4} is to be ascribed to a sluggish release of the drug from the ointment base. No more effective a concentration of the drug is to be expected to reach the fluid recesses of the wound from such ointments than from internal administration.^{5, 6}

systemically administered, fares no better; it has imposed upon it the same limitation of toxicity as when locally applied and is only successful in controlling the invasive infection of the streptococcus.

All of these agents, even including the most promising—the sulfonamides—have been discarded because of their toxicity or failure, and without elucidating the rôle which the burn slough of the wound plays in the growth of the bacteria. The necrotic tissue coagulum, deprived of its blood supply, should be fertile soil. It is also conceivable that this coagulum is impervious to antibiotic agents while at the same time permitting penetration of the bacteria; or it might contain drug inhibitors similar to those of the sulfonamides encountered in pus.

Such were the tools and the understanding of their abilities for attempting the control of infection at the time of the advent of penicillin. It was tempting to hope that penicillin would succeed where the sulfonamides had failed since it was reported nontoxic at any dosage and had wider specific antibacterial properties. The absence of toxicity at any dosage level would be peculiarly valuable for the extensively burned patient threatened with dehydration. The initial experience with penicillin in patients with infections other than burns showed it to have a specificity against the streptococcus equal to that of the sulfonamides as well as a specificity against the staphylococcus. It was wise however in view of the disappointing performance of the sulfonamides to be wary of penicillin's power to control the infection of the full-thickness burn wound.*

In our wariness of penicillin and desire to achieve the earliest possible healing of the full-thickness burn wound it was decided to combine the use of penicillin with prompt surgical excision and grafting of the wound. Surgical excision of the full-thickness burn wound should reduce the number of contaminating bacteria and eliminate necrotic tissue. The base left after excision would undoubtedly be contaminated, but since it would be composed of viable cells, any graft laid upon it would not only prevent further contamination but should proceed to heal without being forestalled by infection. To have the ideal base upon which to place the graft, excision of the burn wound down to viable tissue should be done immediately after injury. With the passage of time the contaminating bacteria within the burn slough would have a chance to multiply and, therefore, the longer the delay after injury, the greater the number which would inevitably be transferred to the excised base during the operative procedure. Also, with the passage of time an inflammatory reaction would appear beneath the necrotic skin in the living

* It is not possible by quoting the literature available in 1943, the time when this project was initiated, to give proper credit for the ideas and help upon which we drew freely. Information available at that time and currently throughout the war was promptly disseminated by bulletin to each group of investigators by the Office of Scientific Research and Development. An adequate survey of the literature is not intended. In the setting-up and conduct of this project, we are particularly indebted for advice to Dr. Champ Lyons, Dr. Rene J. Dubos, Dr. Chester S. Keefer, and Dr. Frank L. Meleney.

tissues which form the base left after excision. Any inflammation should be unhealthy for the successful take of the graft.

The full-thickness burn wound of limited extent has been excised immediately after injury and the defect closed with a graft. The excision and grafting of extensive full-thickness wounds has had to be delayed because of the precarious physiologic state of the patient and because unburned skin for the grafting was lacking. The excision and grafting of both circumscribed and extensive wounds has also been delayed because this project was set-up with the needs of the Armed Services in view and because the postulated conditions of warfare indicated that it would not be possible to operate immediately upon a burn casualty. The delay facing the casualty suggested that an arbitrary interval of from four to seven days between injury and excision and grafting should be tried in some of the cases.⁷

Penicillin was administered systemically to all patients whether excision and grafting was immediate or delayed. Although, admittedly, two therapies were being tried at the same time, and it might prove difficult to ascribe to each its share of credit, the drug was given advisedly to give the operation all possible support and, in those patients in whom time was allowed to elapse between injury and surgical excision, to afford the opportunity to judge the efficacy of penicillin in holding infection in abeyance.

The study has included a comprehensive survey of the bacterial flora of burn wounds and its alteration under penicillin therapy and of certain changes in metabolism of the organisms, such as the development of a resistance to penicillin during the course of its administration. Dissemination of the organisms of the wound through the blood stream and urinary tract and certain aspects of the metabolic response of the host, including the development of a specific immunity, have been studied as well.

Penicillin was not withheld from alternate cases for purposes of control; it was believed that those patients with comparable wounds who had been treated with sulfadiazine systemically in the year previous would serve as acceptable controls. The majority of these patients were those studied under the Contaminated Wound Project of Doctor Meleney by Drs. Champ Lyons and F. W. Rhinelander at the Massachusetts General Hospital.⁸ The bacteriologic technics of Doctor Lyons and this study were identical.

To achieve clarity of presentation the data of the study have been divided into four papers. In the first, the nature of the bacterial contamination and subsequent flora found in partial and full-thickness burn wounds in patients treated with either penicillin or sulfadiazine is described. In the second, the natural occurrence among bacteria of penicillin resistance and inhibition and the development of penicillin resistance in the flora of the burn wounds of patients treated with penicillin is recounted. Presented in the third and fourth papers are the aspects peculiar to the staphylococcus and streptococcus. Brief comments only are made in conclusion of the first three parts. Discussion of the observations, including the clinical significance, is delayed until the end of the fourth part.

METHODS

Immediately upon entry to the hospital, each patient was placed in an isolation room in the Emergency Ward where every precaution was taken to avoid further contamination. The burn wounds were inspected, their location and depth charted. They were then covered, without débridement or cleansing, with a firm protective dressing of petrolatum impregnated, fine-meshed gauze, thick dry cotton and an elastic bandage or a towel. Subsequent changes of dressing were made in an operating room under aseptic precautions.

The patients were accommodated in single rooms on an isolation floor where supervising nurses were in constant attendance. Occasional bacterial counts of the air in these rooms showed a number and variety of organisms comparable to those recovered from the air of single rooms on a floor caring only for uninfected surgical cases; from the air of rooms in another part of the hospital containing infected cases cared for without special precautions were recovered a wider variety of pathogenic organisms with more than ten times the number of colonies.*

The burns were arbitrarily divided into areas or "wounds." A culture was taken of each wound on admission and at each subsequent change of dressing until healing occurred. The cultures taken on the day of injury (O-day) in the majority of the sulfonamide-treated cases were of dead epidermis removed from the wounds. All other cultures, including those of O-day of the penicillin-treated, and the remainder of the sulfonamide-treated cases, were taken by rubbing the exposed surface of the wound with dry sterile cotton swabs.

The technics used for isolation and identification of the organisms were essentially those established by Meleney⁸ for the various units of the Contaminated Wound Project under the Committee on Medical Research of the Office of Scientific Research and Development. Anaerobiasis was secured by the chromium-sulfuric acid method of Rosenthal,¹¹ as modified by Mueller and Miller.¹²

Isolation and identification of all morphologic types, seen microscopically, were attempted, selective media, especially those for the suppression of gram-negative bacilli,¹³ being resorted to when necessary. The gram-negative bacilli

* Colebrook,⁹ and Cruikshank¹⁰ have repeatedly called attention to the frequency of the spread of organisms from one burned patient to another on an open ward. Strains of streptococci, recognizable by their Griffith-type and sulfonamide resistance, were traced in the wounds and also in the dust of the room. It was in order to reduce such cross and continued contamination that the patients included in the present study of wound flora were cared for in isolation rooms under special precautions and had their dressings changed, each wound separately, with aseptic technic only in the operating room. These precautions resulted in some patients in preventing an organism, for example a staphylococcus, from spreading from one wound to an adjacent one in the same patient. On the other hand, in spite of all precautions, evidence was occasionally obtained of the spread of a bacterial strain from one patient to another. A morphologically typical diphtheroid, causing a green discoloration of blood agar with a fruity odor on growth, first isolated from one patient, spread during the course of two weeks to three other patients.

were identified to the genus. The presence of aerobic gram-positive sporulating and nonsporulating (diphtheroid) bacilli was merely recorded. The staphylococci were also examined for color, production of hemolysis on five per cent horse blood agar, and the power to coagulate normal human plasma; the streptococci for type of hemolysis produced on five per cent horse blood agar, the Lancefield groups (A, B, and C, only) if *beta* hemolytic, and "d্রেft" (bile) solubility for differentiation from the pneumococcus if *alpha* hemolytic¹⁴; and the *Clostridia* for species, as far as possible according to Spray's "Tentative Key to the Sporulating Anaerobes."¹⁵

OBSERVATIONS

The data to be given in this study of bacterial flora of burn wounds are limited to those obtained from patients who were in the hospital, and under observation, from the time of onset of chemotherapy until the wounds were healed or the study ended. Fifty-four patients were observed under systemic penicillin therapy and 38 under systemic sulfadiazine; these latter are the controls for the penicillin therapy. No patients were observed for any length of time who did not receive either form of chemotherapy; there are, therefore, no controls for both penicillin and sulfadiazine.

The penicillin dosage was relatively low in the first cases (100,000 units or less per day) and high in the later cases (250,000 to 500,000 units per day); in a few cases nearly 1,000,000 units per day were given over short periods. Sodium penicillin only was used; it was injected intramuscularly usually, occasionally intravenously. The dosage schedule for the intramuscular injections varied from two to four hours.

In the patients receiving sulfadiazine, the dosage was regulated by the blood level; it was maintained between 6 and 12 mg./100 cc. If a patient showed sensitivity to the drug it was stopped and the patient was dropped from the bacteriologic study at that time.

Cultures were obtained once a week from nearly all of the wounds; culturing was abandoned only when the wound was healed.

In addition to the study of the flora of the wound, the effectiveness of the penicillin therapy was also judged in certain cases by study of those of the blood stream and urinary tract.

(1) FLORA OF FULL-THICKNESS BURN WOUNDS UNDER PENICILLIN THERAPY (CHARTS 1A-C)

Twenty-eight patients with 80 full-thickness burn wounds were observed in the hospital from the day of injury until healing. Penicillin was administered to the patients for at least 49 days unless all of the wounds of a patient were healed before this time. The wounds were of varying extent. Some wounds were excised and grafted promptly; the grafting of others was delayed until after spontaneous separation of the slough. All cultures were planted from swabs which had been rubbed firmly on the wounds.

On the day of injury (O-day) an average of almost three bacterial strains

was recovered from each wound; from the 69 wound cultures on O-day 199 strains were recovered (Chart 1A). In the first two weeks there was an abrupt increase in the number of strains recovered so that by the 14th day an average of five strains was recovered from each wound (72 wounds cultured, 368 strains recovered). From the 3rd to the 7th weeks there was a gradual decrease in the number of all bacterial strains recovered, reaching an average of 4.2 strains per culture on the 49th day.

The increase in number of strains recovered in the first two weeks is primarily a reflection of an increase in the number of the streptococci and gram-negative bacilli, and to a less extent of the diphtheroids and aerobic spore forming organisms (*B. subtilis*) (Charts 1B and 1C). The gram-negative bacilli, after an abrupt rise in incidence in the first two weeks, continued to increase very little. The streptococci, after an initial abrupt increase, remained stationary in incidence during the remaining period of observation. The number of strains of *Clostridia* recovered varied but little over a period of seven weeks after a slight early increase. The strains of the staphylococci showed a slow and steady decrease in incidence throughout the period of observation.

The flora of the full-thickness wounds of patients who were admitted later than the day of injury but who had received no chemotherapy previously were also studied throughout a course of penicillin therapy which was started on admission and lasted for 42 days. Thirty-nine wounds in 19 patients who were admitted from 1 to 30 days after injury (average 7.2 days) were studied (Chart 2). The wounds varied in extent as did the amount of infection clinically apparent in the wound on entry and before chemotherapy. There was usually present a severe localized infection and occasionally an invasive process with cellulitis and lymphangitis. One patient had a positive blood culture of a *Staph. albus*. With the subsidence of the clinical infection, some of the wounds were excised and grafted. The cultures were by means of the swab technic.

The number of all bacterial strains recovered on admission was slightly lower than that found on the 7th day in the patients who were admitted and treated with penicillin beginning on the day of injury. Following onset of therapy there was immediately a decline rather than a rise in number. It was not until after the 30th day of therapy that the number of strains rose to that encountered in the previous group.

The incidence of certain individual bacterial strains was significantly either different from or similar to that encountered in the patients receiving penicillin from the day of injury. Of the differences, the staphylococci were found more often on the day of entry than at any time in those patients treated from injury; following onset of penicillin there was a sharp decline to the number of the previous group. The streptococci were also more often recovered and at their maximum on the day of entry. The incidence, however, of both *Clostridia* and the gram-negative bacilli was similar in the two groups of cases. The *Clostridia* scarcely varied while the gram-negative bacilli starting

FLORA OF 3° BURNS - SYSTEMIC PENICILLIN
80 WOUNDS IN 28 PATIENTS

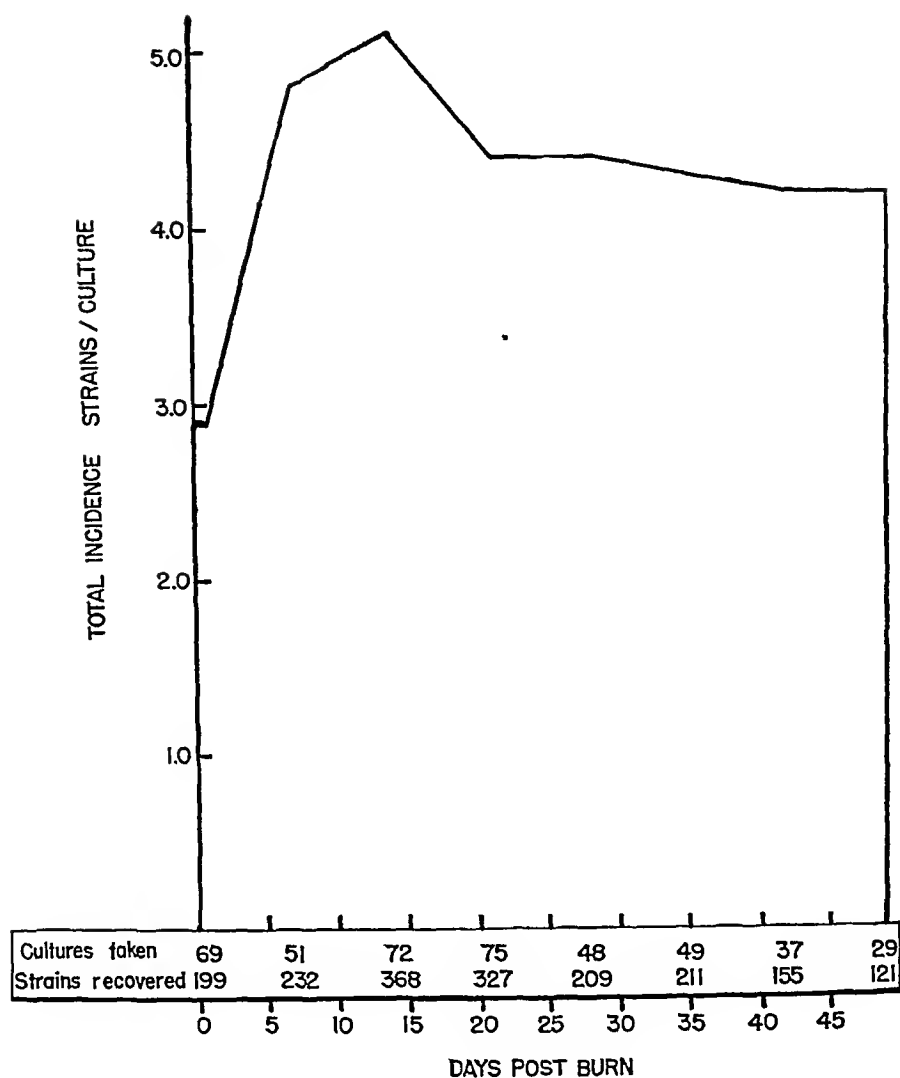


CHART 1A

CHART 1.—The Bacterial Flora of Full-thickness Burn Wounds in Patients Receiving Penicillin Therapy: Eighty wounds of 28 patients were followed from O-day through the 49th day unless healing had occurred previous to this time. Cultures were by the swab technic. The number of cultures planted on O-day, and within each subsequent seven-day period, and the number of strains recovered in these cultures are given at the bottom of each chart. Systemic penicillin was started on O-day and continued throughout the period of observation.

(A) Incidence of All Strains in All Cultures (Total Incidence: Strains per Culture): The abrupt increase in number of bacterial strains in the first two weeks and subsequent gradual decrease is evident.

BACTERIOLOGY OF BURN WOUNDS

FLORA OF 3° BURNS - SYSTEMIC PENICILLIN

80 WOUNDS IN 28 PATIENTS

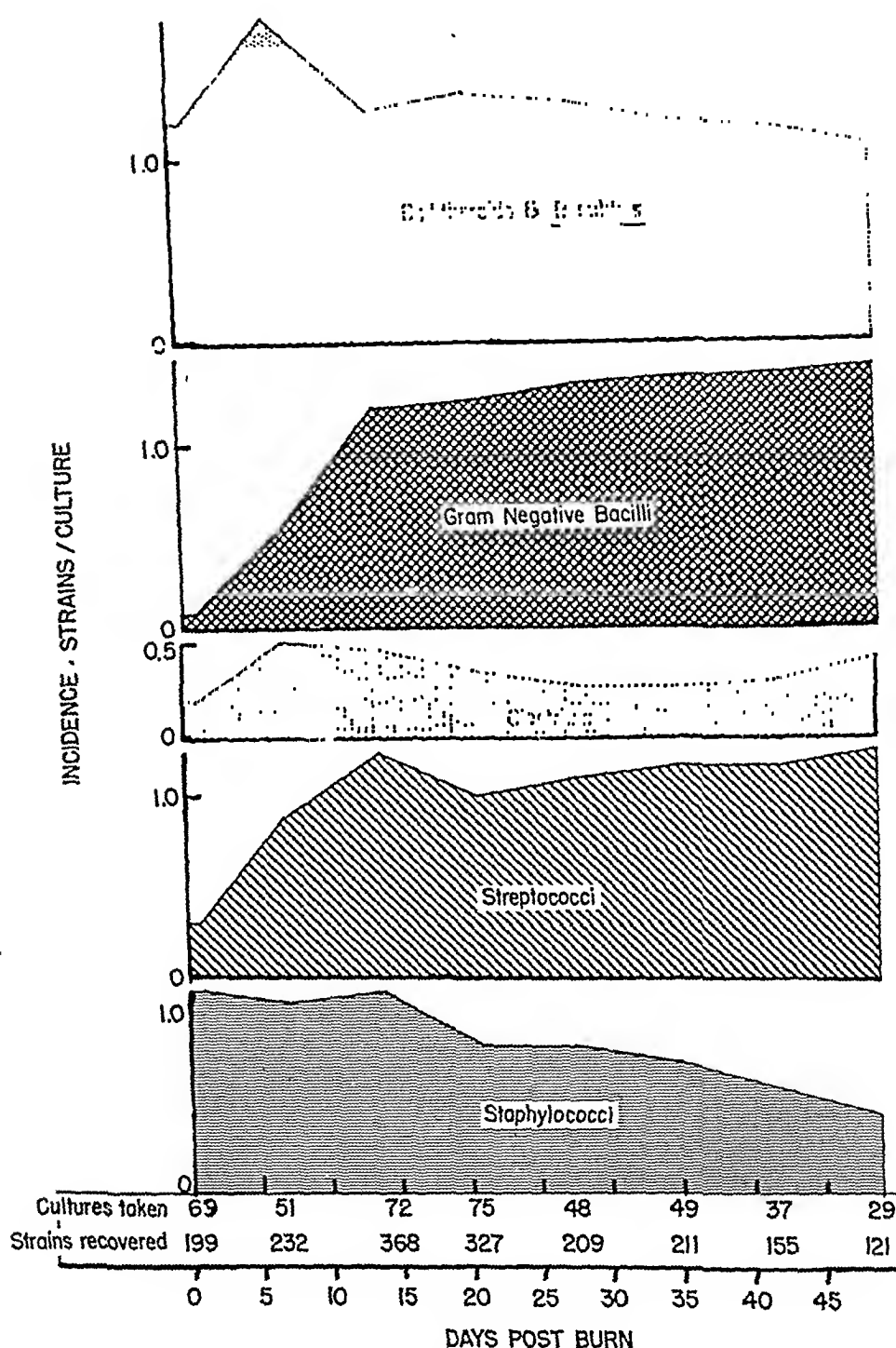


CHART 1B

CHART 1(B).—The Strains Recovered Plotted as Incidence or Number of Strains per Culture: Each strain is plotted in its appropriate bacterial group. The number of strains of staphylococci averaged slightly more than one per culture at entry and decreased gradually throughout the period of observation to less than one strain for every two cultures. The number of strains of streptococci, low on O-day, increased abruptly in the first two weeks and thereafter remained stationary in frequency. *Clostridia* were seldom recovered, and their incidence varied but little. Gram-negative bacilli, almost absent on O-day, increased abruptly in the first two weeks but only gradually thereafter. The incidence of diphtheroids and aerobic spore-formers (*B. subtilis*) increased slightly during the first week and gradually declined subsequently.

with but few increased abruptly in the second week of penicillin therapy and only slowly thereafter.

Bacteriuria.—A number of the patients with full-thickness wounds who were receiving systemic penicillin therapy developed signs and symptoms of lower urinary tract infection. The urine of several of these patients was cultured; various organisms, including gram-positive, were found but they were always of species present in the wounds of the same patient. All of the patients developing the infection had previously had in-dwelling catheters or been catheterized. The incidence of bacteriuria and urinary infection was not determined since the urine of the patients was not routinely cultured.

Bacteremia.—Blood cultures were made on 12 of the extensively burned patients, on 11 while they were receiving penicillin and on the 12th on the 2nd day after injury and before starting chemotherapy. This last patient and five of those on penicillin proved to have organisms in their blood. Four white staphylococci (2 coagulase-negative, 2 coagulase-positive), 2 *Clostridia* and 1 *B. proteus* were recovered. The same organisms were recovered from the wounds of the patient in each instance.

Most of the patients were sufficiently ill to arouse suspicion of invasive infection and the blood cultures were therefore taken. Two of the positive blood cultures found during the course of penicillin therapy were taken on the day after injury for chance information; both were positive, one showing *Clostridia* only, the other *Clostridia* and a *Staph. albus*, coagulase-negative. The cultures on the other eight were made at times of crisis; three were positive, two showing white staphylococci, coagulase-negative and positive, and the third *B. proteus*. The blood of the 11th case, cultured on the second day after injury, and before onset of penicillin therapy, contained a *Staph. albus*, coagulase-positive. A survey of the incidence of bacteremia in burns was not made.

(2) FLORA OF FULL-THICKNESS BURN WOUNDS UNDER SULFONAMIDE THERAPY (CHART 3)

The flora of 46 full-thickness burn wounds were studied in 25 patients who received sulfonamide therapy starting on the day of injury. Only 13 of the wounds were cultured on this day, and before the onset of chemotherapy, since 13 of the patients were victims of the Coconut Grove fire and the exigencies of their care discouraged the taking of cultures.¹⁶ Sulfadiazine only was used systemically; a few patients had certain other sulfonamides applied locally at various dressings. The wounds were of varying extent. The first grafting was performed on the 24th day after injury when the slough had separated spontaneously. All wounds were followed as long as the patients were receiving systemic sulfonamides, or until healed. The 13 wound cultures accomplished on O-day were made from dead epidermis. All subsequent cultures were planted from swabs which were pressed firmly on the wounds in the manner used in the penicillin-treated patients.

The interpretation of the trend of the incidence of bacterial strains

BACTERIOLOGY OF BURN WOUNDS

recovered under sulfonamide therapy depends upon the significance ascribed to the numbers recovered in the cultures taken on O-day. A decrease in all bacterial strains in the first two weeks is shown (Chart 3). This is in contrast to the observations under penicillin therapy but its significance is to be discounted because of the discrepancies in the methods of culturing on O-day in

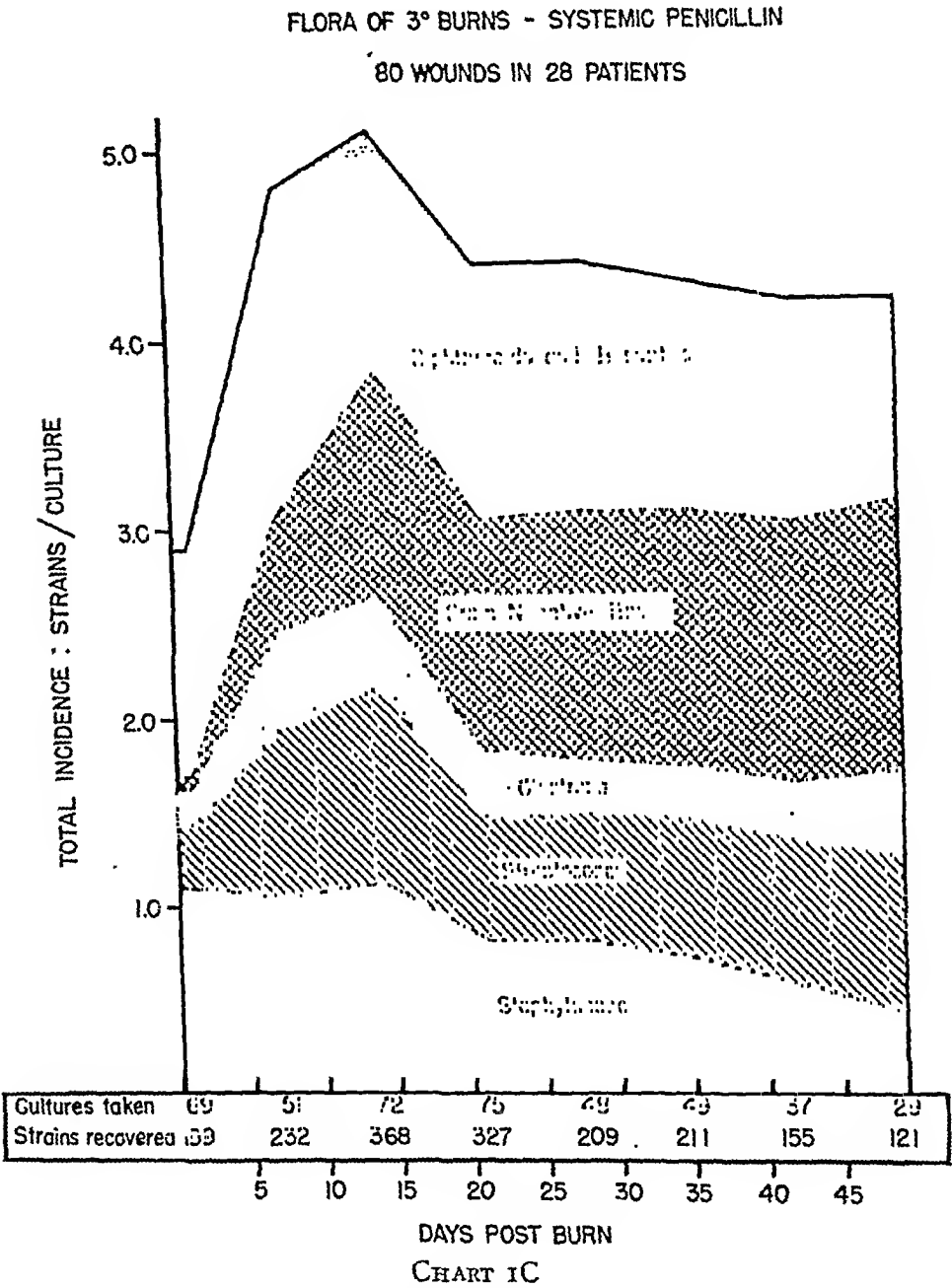


CHART 1(C).—Composite of Charts 1A and B: Both the Incidence of Strains in the Individual Bacterial Group and the Part which each Plays in the Total Incidence: The top (heavy) line shows the incidence of all strains recovered and is in the identical position as in Chart 1A. The area occupied by each bacterial group is planometrically the same as that in Chart 1B. The zero line of each group other than that occupying the bottom position (staphylococci in this instance) is distorted by the top line of the group or groups beneath. (All of the subsequent charts of bacterial incidence are composed in this manner.)

the two groups and because the number of sulfonamide-treated patients cultured on O-day was small (only 12 patients with 13 wounds).

If one discounts the O-day findings then the incidence of bacterial strains shows a slow decrease in number in the first 35 days with an increased num-

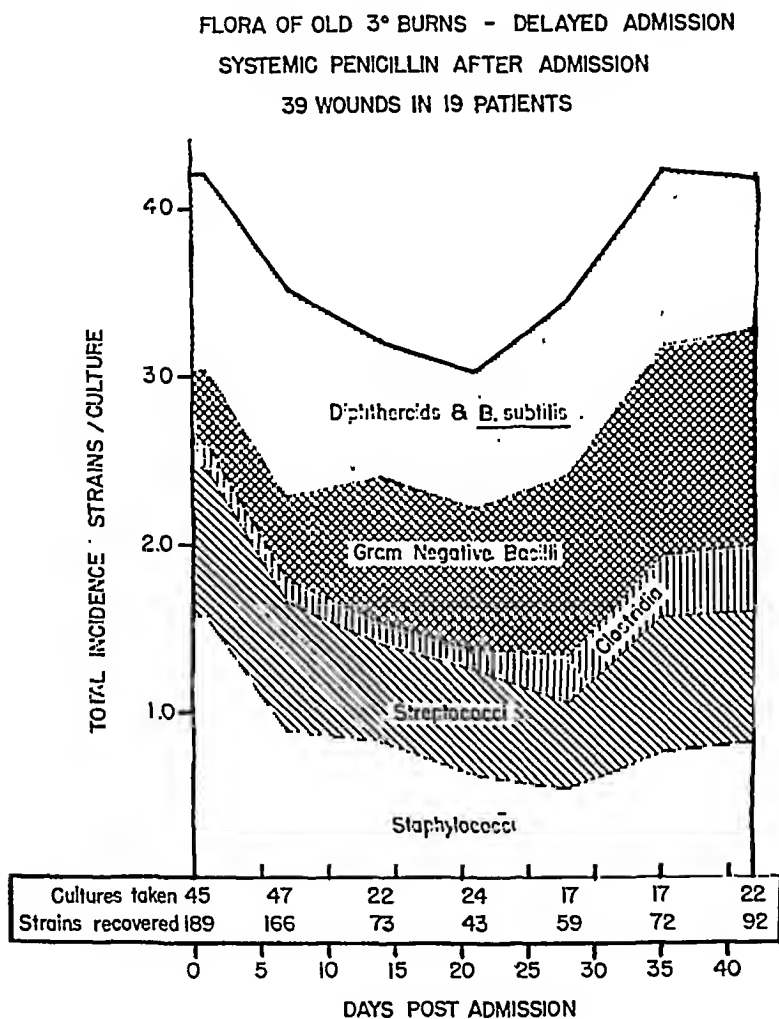


CHART 2

CHART 2.—The Bacterial Flora of Full-thickness Burn Wounds in Patients whose Hospital Admission and Penicillin Therapy were Delayed: Thirty-nine wounds of 19 patients were followed from day of entry to the 42nd hospital day unless healing had previously occurred. Admission varied from 1 to 30 days after injury (average 7.2 days). Cultures were by the swab technic. The number of cultures planted and strains recovered are given at the bottom of the chart, as in Chart 1, and all subsequent charts of bacterial incidence. Penicillin was started on the day of admission and continued throughout the period of observation.

ber later. The incidence of the staphylococci ran parallel to that of all bacterial strains. There is a consistent slow decline in the number of the streptococci with their complete disappearance on the 55th day. The *Clostridia* varied in incidence but little throughout the period of observation except for

BACTERIOLOGY OF BURN WOUNDS

disappearance on the 55th day. There is a gradual increase in the incidence of the gram-negative bacilli; it is slower than that encountered under penicillin therapy. The incidence of diphtheroids and aerobic spore-forming organisms (*B. subtilis*) fluctuated to some degree but the changes are probably not significant.

(3) FLORA OF PARTIAL-THICKNESS BURN WOUNDS UNDER SULFONAMIDE THERAPY (CHART 4)

The bacterial flora of 58 burn wounds of partial-thickness destruction were studied in 35 patients treated with sulfadiazine systemically. The

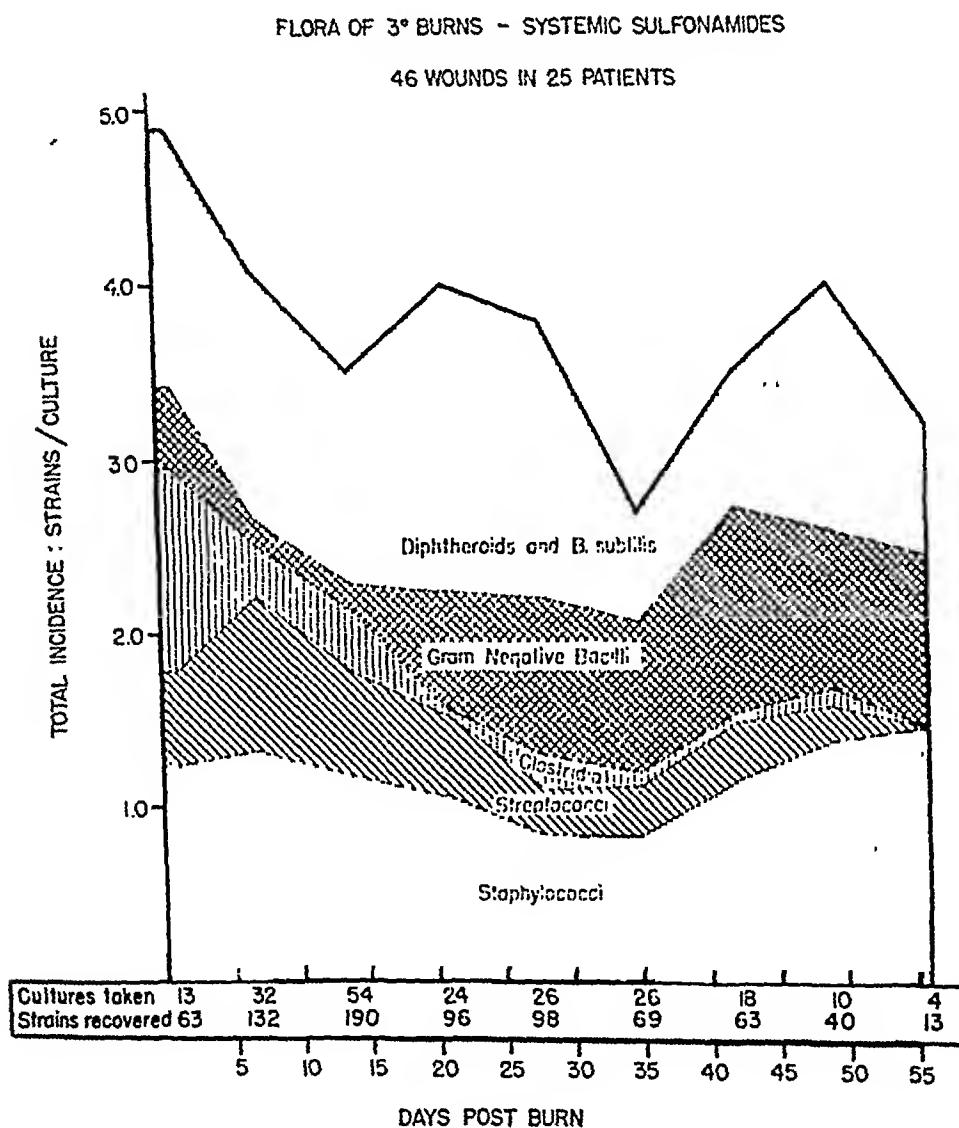


CHART 3

CHART 3.—The Bacterial Flora of Full-thickness Burn Wounds in Patients Receiving Sulfonamide Therapy: Forty-six wounds of 25 patients were followed from day of injury to the 56th day, or until healed; however, 33 wounds of 13 patients (all victims of the Coconut Grove fire) were not cultured on the day of injury. Most of the cultures on the day of injury were of dead epidermis; all others were by swab technic. Sulfadiazine was started systematically on the day of injury and continued throughout the period of observation.

patients entered the hospital on the day of injury and were followed for not longer than 21 days. But 29 of the wounds were cultured before the onset of chemotherapy because 16 of the patients (with 29 wounds) were victims of the Coconut Grove fire. The wounds were of varying extent; all were open with ruptured blisters. The depths varied from superficial to deep

FLORA OF 2° BURNS - SYSTEMIC SULFONAMIDES

58 WOUNDS IN 35 PATIENTS

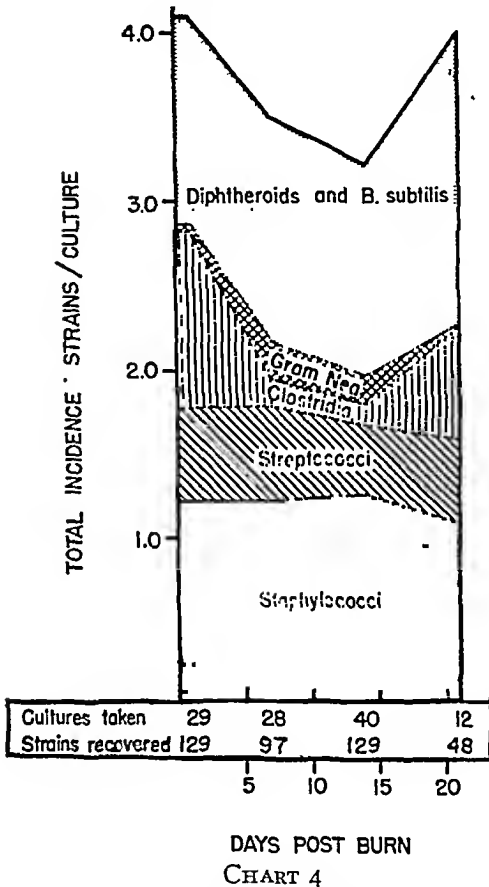


CHART 4

CHART 4.—The Bacterial Flora of Partial-thickness Burn Wounds in Patients Receiving Sulfonamide Therapy: Fifty-eight wounds of 35 patients were followed from day of injury to the 21st day, or until healed; however, 29 wounds of 16 patients were not cultured on day of injury. The majority of the cultures on the day of injury were from dead epidermis; all others were by swab technic. Sulfadiazine was started systemically on the day of injury and continued throughout the period of observation.

injury and were followed until the 21st day, or until healed. The cultures were all by swab technic.

The pattern of the bacterial strains recovered in the three weeks' period from injury to healing paralleled, in general, that of the first three weeks of the full-thickness burn wounds under penicillin therapy (Chart 5; cf. Chart 1).

intermediate- or almost full-thickness. In addition to the systemic sulfadiazine, sulfonamides were applied locally to a few of the wounds at the initial and later dressings. The majority of the 29 wound cultures made on the day of injury were grown by dropping dead epidermis into the culture medium; thereafter all cultures were made from swabs.

The incidence of all bacterial species encountered approximates that of the full-thickness wounds under sulfonamide therapy (Chart 4; cf. Chart 3). The only significant differences found in the partial- as compared with the full-thickness wounds are a slightly lower initial contamination and an increase in the third week in the incidence of the *Clostridia*.

(4) FLORA OF PARTIAL-THICKNESS BURN WOUNDS UNDER PENICILLIN THERAPY (CHART 5)

The bacterial flora of 35 wounds of partial-thickness were studied in 18 patients who were receiving penicillin systemically. The wounds were of varying extent, all open and ruptured blisters, and were of varying depths from superficial to nearly full-thickness. All were cultured on

The differences noted are that the number of strains recovered throughout were fewer, that the increase in number of strains in the first two weeks is numerically less and that neither the streptococci nor the *Clostridia* increased at all in incidence. What increase there was in bacterial strains, therefore, is accounted for by the increase in gram-negative bacilli and diphtheroids and *B. subtilis*.

It is to be noted that although there was no significant change in incidence of the gram-negative bacilli in the wounds of partial-thickness in the patients under the sulfonamides, the same rapid increase in numbers as in the full-thickness wounds took place in the partial-thickness wounds in the first 14 days under penicillin.

(5) DISTRIBUTION OF FLORA ACCORDING TO BODY AREA

In order to see whether the quality of the bacterial contamination differs in various body areas, influenced perhaps by proximity to the mouth or anus, the flora encountered in wounds of the head and neck, upper, and lower extremities have been separately listed (Table I). Using both partial- and full-thickness wounds of patients receiving no chemotherapy as well as of those receiving penicillin or sulfadiazine, there are available for this analysis 35 wounds of the head and neck, 105 of the upper extremities and 65 of the lower extremities. To permit differentiation of the initial contamination from that occurring while in the hospital the flora found on the day of injury and that from the 1st to 14th days after injury have been separately considered.

From this cross-filling of the data it is apparent that wounds of the lower extremities were maximally contaminated at the time of entry to the hospital. Of all wounds these also showed the highest initial and subsequent *Clostridial* and *gamma* streptococcal infestation. Wounds of the head and neck showed the lowest initial contamination. Wounds both of the head and neck and of the upper extremities partook of the over-all increase in number and varieties

FLORA OF 2° BURNS - SYSTEMIC PENICILLIN

35 WOUNDS IN 18 PATIENTS

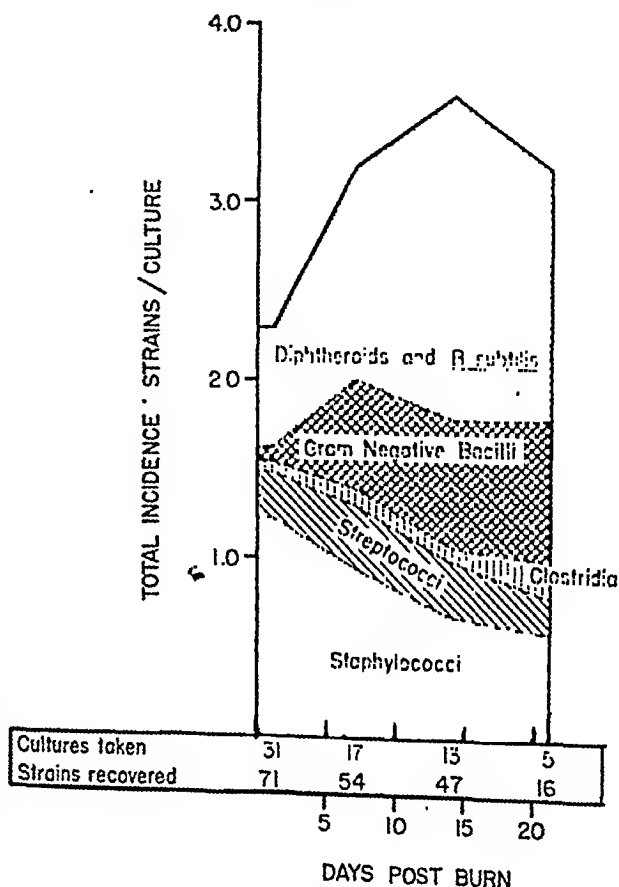


CHART 5

CHART 5.—The Bacterial Flora of Partial-thickness Burn Wounds in Patients Receiving Penicillin Therapy: Thirty-five wounds of 18 patients were followed from the day of injury to the 21st day or until healed. Cultures were by Swab technic. Systemic penicillin was started on the day of injury and continued throughout the period of observation.

of bacterial strains in the first two weeks but the strains were throughout more abundant in the wounds of the upper extremities. In the wounds of the head and neck, *Clostridia* were least often encountered, but one-third as often as in the leg wounds, and, again in contrast to the legs, no *gamma* streptococci were recovered.

Of the other streptococci, not a single *beta* streptococcus was recovered from the 54 cultures taken on the day of injury from wounds of the upper extremities, yet the occurrence and distribution of the *alpha* streptococci in all wounds and at all times were remarkably even; it was the most common streptococcus found.

TABLE I
COMPARATIVE FLORAS OF BURN WOUNDS OF DIFFERENT BODY AREAS
PARTIAL AND FULL-THICKNESS BURN WOUNDS
SULFADIAZINE OR PENICILLIN

Body Area	Head and Neck		Upper Extremities		Lower Extremities	
	35		105		65	
Number of wounds.....						
Day postburn.....	0	1-14	0	1-14	0	1-14
Cultures taken.....	12	54	54	139	41	102
Strains recovered.....	39	202	182	563	167	423
Incidence of strains (strains per culture).....	3.2	3.7	3.4	4.1	4.2	4.2
Percentage of Strains Isolated						
Diphtheroids and <i>B. subtilis</i> ...	35.9	37.6	39.1	36.8	36.5	34.0
Gram-negative bacilli.....	2.6	9.9	3.3	6.9	3.0	9.6
<i>Clostridia</i>	5.1	3.0	13.7	6.2	15.6	9.6
Streptococci:.....	15.3	14.8	12.6	17.8	12.6	20.2
<i>Beta</i> streptococci.....	2.6	4.0	0	3.0	1.8	3.1
<i>Alpha</i> streptococci.....	12.7	10.8	12.6	12.3	10.2	12.8
<i>Gamma</i> streptococci.....	0	0	0	2.5	0.6	4.3
Staphylococci:.....	41.1	34.7	31.3	32.3	32.3	26.6
<i>Staph. aureus</i> , Coag. +.....	2.6	20.3	3.3	17.4	3.6	12.1
<i>Staph. albus</i> , Coag. +.....	2.6	1.5	0.6	2.1	1.8	4.1
<i>Staph. aureus</i> , Coag. -.....	7.7	1.0	2.2	2.1	6.6	0.9
<i>Staph. albus</i> , Coag. -.....	28.2	11.9	25.2	10.7	20.3	9.5

Contrary to the slow decline in number of strains of staphylococci found generally, including the wounds of head and neck and legs, there was no decrease in number in the wounds of the upper extremities. The increase in gram-negative bacilli is more prominent in wounds of the head and neck and lower extremities than in those of the arms.

CONCLUSIONS

In a study of the effectiveness of systemic chemotherapy in the control of the infection of burns, the appearance and subsidence of invasive infection has been observed and a comparison of the bacterial flora of burn wounds made in patients receiving either penicillin or sulfadiazine. These chemotherapeutic agents were found to exert a limited but different control of the organisms in the wound.

Statistical analysis of the influence of chemotherapy upon invasive infection has not been possible because of the difficulty in judging objectively its presence in the burn wound. The effectiveness of penicillin and sulfadiazine on invasive infection remains, therefore, a clinical impression. It will be discussed at the end of the fourth part.

The study of the bacterial flora of the burn wounds is objective, detailed and subject to analysis. Neither sulfadiazine nor penicillin obliterated bacteria in a burn wound. The lesser number of bacterial strains recovered in wounds of partial-thickness compared with those of full-thickness, under either penicillin or sulfadiazine, suggests that there are unknown influences in the full-thickness wound, presumably related to the amount of dead tissue, limiting the action of these chemotherapeutic agents.

In patients receiving penicillin the number of bacterial strains recovered from the wounds increased rapidly in the first two weeks after injury; from the wounds of full-thickness destruction the number of strains subsequently recovered was slightly higher than in the comparable wounds of patients receiving sulfadiazine.

Penicillin exerted a more decisive brake than sulfadiazine on the growth of staphylococci. In the wounds of patients treated with penicillin from the time of injury, the number of strains of staphylococci slowly declined, while in those of patients receiving sulfadiazine the number of strains did not vary. In patients in whom penicillin therapy was delayed the number of strains of staphylococci before therapy was the highest observed; following onset of penicillin there was a prompt fall in the number recoverable.

There was an abrupt rise in the number of strains of gram-negative bacilli recovered from the wounds of patients receiving penicillin in the 2nd week of therapy. That this rise did not appear before onset of therapy in patients in whom the penicillin was delayed and did appear in the same time sequence following administration of penicillin and that this early rise was not observed in the sulfadiazine-treated patients, suggests that the penicillin was responsible for this profusion of gram-negative organisms.

The number of strains of streptococci was held lower by sulfadiazine than by penicillin. The nature of this control is described in detail in the fourth part.

The wounds of certain body areas showed different bacterial contamination. Wounds of the lower extremity on the day of injury already showed the maximal number and variety of strains encountered. The *Clostridia* and the *gamma* streptococcus, organisms commonly found in the colon, were more often found in these wounds than in those of other areas.

From wounds of the head and neck the least number of bacterial strains was recovered on the day of injury. The number from the wounds of the upper extremity lay midway between that of the head and neck and of the lower extremity. No *gamma* streptococci were found initially in the wounds of either head and neck or upper extremities and no *beta* streptococci in the wounds of the latter area.

In seeking the source of the bacteria contaminating burn wounds it should be pointed out that the flora found in the three wound areas on the day of injury are reminiscent of the resident flora expected. Fecal organisms should be more prevalent on skin near the anus. Skin of the hands has been shown by Colebrook and Maxted,¹⁷ to have the power to rid itself of the *beta* streptococcus. It is tempting, therefore, to assume that the organisms found

are the resident flora which survive the burn. If this were true the greater number of strains of organisms should have been found in the less deeply burned wounds rather than in those of full-thickness. This not being so, the resident flora may have been killed by the burn and the contaminating bacteria may have been transported from a location close to the wound, such as the clothing, or from the original source, as the anus itself.

Even if the quality of the flora found on the day of injury tends to exclude dust or other chance contamination as the principal source of the original bacteria, the inadvertent transfer of organisms from the wound of one patient to that of another, which has been observed in the hospital in spite of strict precautions, points-up the necessity of stringent regulations for the care of burn patients.

REFERENCES

- ¹ Hooker, Donald H., and Lam, Conrad R.: Absorption of Sulfanilamide from Burned Surfaces. *Surgery*, 9, 534, 1941.
- ² Pickrell, Kenneth L.: A New Treatment for Burns: Preliminary Report. *Bull. Johns Hopkins Hosp.*, 69, 217, 1941.
- ³ Gurd, Fraser B., Ackman, Douglas, Gerrie, John W., and Pritchard, J. E.: A Practical Concept for the Treatment of Major and Minor Burns. *ANNALS OF SURGERY*, 116, 641, 1942.
- ⁴ Evans, Everett I., Hoover, M. J., and James, G. Watson, III: The Absorption of Sulfonamides from the Burn Surface. *Surg. Gynec. Obst.*, 80, 297, 1945.
- ⁵ Cope, Oliver: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital. The Treatment of the Surface Burns. *ANNALS OF SURGERY*, 117, 885, 1943.
- ⁶ Cope, Oliver: The Chemical Aspects of Burn Treatment. *J. A. M. A.*, 125, 536, 1944.
- ⁷ Cope, Oliver, Langohr, John L., Moore, Francis D., and Webster, Richard C., Jr.: Expeditious Care of Full-thickness Burn Wounds by Surgical Excision and Grafting. *ANNALS OF SURGERY*, 125, 1, 1947.
- ⁸ Meleney, Frank L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft-part Wounds, Compound Fractures, and Burns, with Special Reference to the Sulfonamides. *Surg. Gynec. Obst.*, 80, 263, 1945.
- ⁹ Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.
- ¹⁰ Cruickshank, Robert: The Bacterial Infection of Burns. *J. Path and Bact.*, 41, 367, 1935.
- ¹¹ Rosenthal, L.: Chromium-sulfuric Acid Method for Anaerobic Cultures. *J. Bact.*, 34, 317, 1937.
- ¹² Mueller, J. H., and Miller, P. A.: A Modification of Rosenthal's Chromium-sulfuric Acid Method for Anaerobic Cultures. *J. Bact.*, 41, 301, 1941.
- ¹³ Owen, Cora R.: Acetic Acid Inhibition of Gram-negative Bacilli in Culture Media. *J. Bact.*, 52, 353, 1946.
- ¹⁴ Larson, W. P.: Personal Communication.
- ¹⁵ Spray, R. S.: Semisolid Media for Cultivation and Identification of the Sporulating Anaerobes. *J. Bact.*, 32, 135, 1936.
- ¹⁶ Lyons, Champ: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital: Problems of Infection and Chemotherapy. *ANNALS OF SURGERY*, 117, 894, 1943.
- ¹⁷ Colebrook, L., and Maxted, W. R.: Antisepsis in Midwifery. *J. Obst. and Gynec. Brit. Emp.*, 40, 966, 1933.

(Continue with Part II)

BACTERIOLOGY OF BURN WOUNDS

PART II

THE DEVELOPMENT OF RESISTANCE TO PENICILLIN BY THE FLORA OF FULL-THICKNESS BURN WOUNDS IN PATIENTS TREATED WITH PENICILLIN SYSTEMICALLY

THE ENCOUNTERING of drug-resistant bacteria in patients during the course of sulfonamide therapy, the report of a comparable development of resistance of organisms to penicillin and of the power of bacteria to inhibit the action of penicillin, prompted the estimation, as an integral part of the study of the bacteriology of burn wounds, of the sensitivity and the development of resistance to penicillin and of the inhibition of penicillin by the bacterial flora. When this study was initiated in 1943 there was evidence that certain types of bacteria, normally sensitive to the sulfonamides, could develop an indifference or resistance to the drug.¹ Grown *in vitro* in media containing increasing concentrations of a sulfonamide, the metabolism of the organisms changed to the extent of becoming inured to the drug and growing without restraint. Such resistance was also believed to develop *in vivo*. Colebrook,² from the burn wounds of patients receiving sulfonamides, recovered first a sulfonamide-sensitive *beta* streptococcus, subsequently a drug-fast organism of the same strain, and reasonably suggested that the fastness had been induced.

When penicillin first became available to civilian Centers in this country, observations were available suggesting that similar development of drug resistance was to be expected during the course of penicillin therapy.^{3, 4} Measurement of the development of resistance or loss of sensitivity should indicate not only the period during which the drug could be expected to be maximally effective but also whether the drug penetrated the burn slough, should the organisms in the slough retain their sensitivity.

Just as the bacteriostatic action of the sulfonamides had been found by several workers to be inhibited by breakdown products of bacteria and cells.¹ so that of penicillin had been reported thwarted by growth of nonsensitive organisms. Abraham and Chain⁵ recorded, in 1940, that the gram-negative bacilli produced an enzyme-like substance which destroyed penicillin, and which they termed penicillinase. Because of the deterring influence which contaminating bacteria might exert through such inhibition, measurement of inhibition by those organisms commonly encountered in the flora of burn wounds was deemed prudent.

METHODS

A first part of the laboratory effort of this study was the development of methods for the measurement of penicillin sensitivity and inhibition. The first test of the bacterial sensitivity to penicillin (Introductory Test), useful as a step in the measurement of bacterial inhibition, proved unnecessarily cumbersome as a routine test and was supplanted by a simpler method (Routine Test).

Bacterial Sensitivity to Penicillin (Introductory Test).—The naturally-occurring penicillin sensitivity of a bacterium was determined by comparing its growth in a medium containing penicillin with that in a penicillin-free medium. Growth was judged by turbidity of the media. Five-cubic centimeter portions of nutrient broth containing 50, 25, 5, 1 and 0 units of penicillin per cubic centimeter were inoculated with 0.1 cc. of an 18-hour broth culture of the organism to be tested and incubated for 18 hours at 37° C. Any strain whose growth was not inhibited by penicillin in the concentrations above five units per cc. was considered to be resistant to penicillin. Any strain whose growth was inhibited by concentrations of five, or less, units per cc. was considered sensitive.

Bacterial Inhibition of Penicillin.—To decide whether a test organism had the power to inhibit the antibacterial action of penicillin, small disks of sterile filter paper which had been dipped into the inoculated broth tubes containing none or varying concentrations of penicillin were laid upon the surface of blood agar plates previously inoculated with a staphylococcus of known high sensitivity to penicillin. (No attempt was made to destroy the test strain growing in the broth tubes.) After incubation at 37° C. for 18 hours the plates were examined for zones of inhibition of the growth of the staphylococcus around the disks. An organism was considered to be a penicillin-inhibitor if the growth of the known staphylococcus on the plate was not inhibited and if the test fluid had come from a tube which had contained five units, or more, of penicillin per cubic centimeter.

Bacterial Sensitivity to Penicillin (Routine Test).—All gram-positive organisms isolated from the patients on penicillin, except diphtheroids and aerobic sporulating bacilli, were tested for sensitivity to penicillin. A five per cent horse blood agar "pour" plate was made with 0.05–0.1 cc. of an 18-hour liquid culture of the organism to be tested and allowed to harden. Filter paper disks, cut with an ordinary paper punch from thin, "rapid filter" type paper and sterilized by dry heat, were dipped into solutions of 50, 25, 5 and 1 units per cc. of penicillin in isotonic saline, drained on sterile gauze sponges, and laid on the surface of appropriately marked segments of the plate. After 18-hour incubation at 37° C., aerobically or anaerobically according to the requirements of the organism under test, the plates were examined for zones of inhibition of growth of the test organism by the penicillin. Strains not inhibited by concentrations of penicillin above five units per cc. were considered resistant and are classified as such in the charts.

OBSERVATIONS

1. *Natural Ability of Wound Bacteria to Resist and Inhibit Penicillin.*—The penicillin resistance and inhibitory power of 207 bacterial strains were studied. The strains were either isolated from patients with various surgical infections or found as contaminants in the laboratory media. Since none of the patients from whom the bacteria were isolated had received penicillin and, indeed, since no patient had been studied up to this time who had re-

ceived penicillin, it was deemed that none of the organisms could have an artificially-induced reaction to penicillin. The findings are summarized in Table II.

Of the 16 strains of streptococci tested, only one (6 per cent) was found to be resistant to penicillin. This was a *beta hemolytic Streptococcus*, Group A-Lancefield, which was not inhibited by concentrations of 50 units of penicillin per cc. of broth and which showed no evidence of inhibitory action against penicillin. (This native resistance of a *beta hemolytic Streptococcus* has not otherwise been encountered in our experience, nor have we found it mentioned in the literature.) One strain (6 per cent), a sensitive *gamma nonhemolytic Streptococcus*, was found to be inhibitory to penicillin.

Of the staphylococci, 8 of 118 strains (7 per cent) were resistant to penicillin; 8 (7 per cent), 6 of the 8 resistant and 2 sensitive strains, inhibited the drug. Five (16 per cent) of the 32 coagulase-positive and four (5 per cent) of the 86 coagulase-negative strains were resistant, a three-fold greater incidence of resistance among the more virulent staphylococci. Of the coagulase-positive strains, none of the 27 sensitive and three of the five resistant organisms (60 per cent) were inhibitory; of the coagulase-negative, two of the 82 sensitive (3 per cent) and 100 per cent of the five resistant strains were inhibitory. Of the 45 *Staph. aureus*, no sensitive and four of the six resistant (67 per cent), and of 73 *Staph. albus* the two resistant and two of the 71 sensitive strains (3 per cent) inhibited the penicillin. Thus, penicillin inhibition by sensitive strains of staphylococci was found only in 2 coagulase-negative *Staph. albus*, both recovered as contaminants on laboratory media; natively resistant strains do not invariably produce penicillin inhibitors detectable by this method.

Nine of 30 diphtheroids (30 per cent) were resistant to penicillin; all of these and three of the 31 sensitive strains (14 per cent) inhibited the drug's action.

Twenty-two of 34 aerobic spore-formers (*B. subtilis*) (65 per cent) were resistant to penicillin and 27 (80 per cent) inhibited its action. One resistant strain did not inhibit, but six (50 per cent) of the sensitive strains did so.

Only nine strains of gram-negative bacilli of the *coli-pyocyaneus-proteus* group were tested at this time. All were resistant to penicillin, and all but the two strains of *B. proteus* were inhibitory. Since that time we have tested four more strains of *B. proteus* and found them to be inhibitory; these were, however, isolated from patients who were receiving the drug.

In summary, there is no absolute correlation between the organisms resistant to the bacteriostatic action of penicillin and those capable of inactivating or inhibiting this agent.

2. *Resistance to Penicillin of the Flora of Full-thickness Burn Wounds in Patients Treated with Penicillin.*—The initial occurrence of resistance to penicillin and its subsequent development was followed in the gram-positive strains recovered from the 80 wounds of the 28 patients with full-thickness burn wounds treated with penicillin from the day of injury. (The wounds and

TABLE II

RESISTANCE TO, AND INHIBITION OF, PENICILLIN BY ORGANISMS NOT PREVIOUSLY EXPOSED TO THE DRUG

Organism	Number of Strains Tested	Penicillin- sensitive		Penicillin- resistant		Penicillin- noninhib- iting		Penicillin-sensitive		Penicillin-resistant	
		Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Total Number	Inhibiting Per Cent	Total Number	Inhibiting Per Cent
<i>Streptococci</i>	16	94	6	6	6	94	93	15	7	1	0
<i>Beta</i>	8	88	12	0	0	100	100	7	0	1	0
<i>Alpha</i>	6	100	0	0	0	100	100	6	0	0	..
<i>Gamma</i>	2	100	0	50	50	50	50	2	50	0	..
<i>Staphylococci</i>	118	93	7	7	7	93	98	110	2	8	75
Coag +.....	32	84	16	9	9	91	100	27	0	5	60
Coag 0.....	86	95	5	6	6	94	97	82	3	5	100
<i>Staph. aureus</i>											
Coag +.....	30	83	17	10	10	90	100	25	0	5	60
Coag 0.....	15	93	7	7	7	93	100	14	0	1	100
<i>Staph. albus</i>											
Coag +.....	2	100	0	0	0	100	100	2	0	0	..
Coag 0.....	71	97	3	6	6	94	97	69	3	2	100
<i>Diphtheroids</i>	30	70	30	47	47	53	86	21	14	9	100
Aerobic spore-formers.....	34	35	65	79	79	21	50	12	50	22	96
Gram-negative bacilli.....	9	0	100	78	78	22	..	0	..	9	78
Total.....	207										

BACTERIOLOGY OF BURN WOUNDS

patients are the same as those studied under section one (Chart I) of Part I.) The sensitivity of a few strains, mainly *Clostridia*, which were difficult to grow and isolate, was not observed. The penicillin sensitivity of diphtheroids, *B. subtilis*, and gram-negative bacilli was, also, not observed. It was taken for granted from the previous studies that the diphtheroids and *B. subtilis* groups were 50 per cent penicillin-resistant, and the gram-negative

DEVELOPMENT OF PENICILLIN RESISTANCE IN 3° BURNS
80 WOUNDS IN 28 PATIENTS

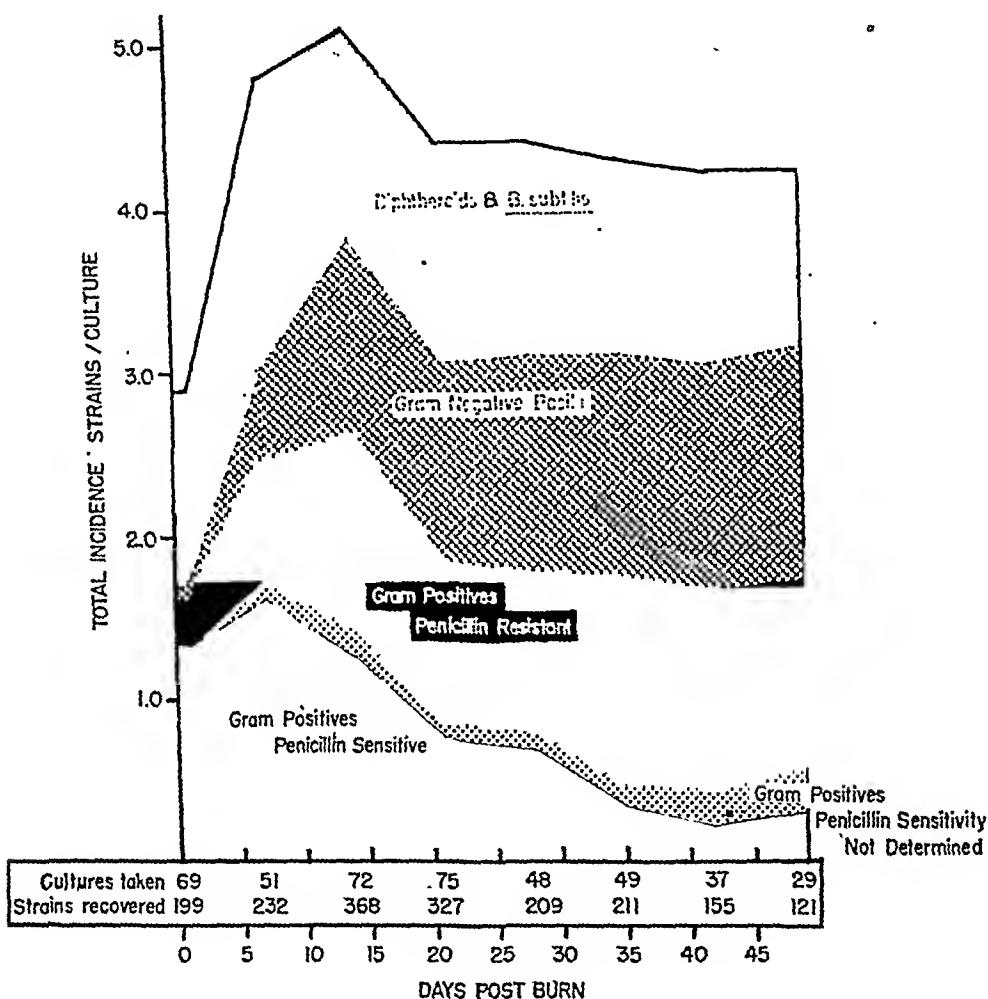


CHART 6

CHART 6.—The Occurrence of Penicillin Resistance in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: Eighty wounds of 28 patients (cf. Chart 1 of Part I) were followed from the day of injury throughout a course of penicillin therapy. All gram-positive organisms, except diphtheroids and aerobic spore-formers (*B. subtilis*), were tested for sensitivity to penicillin. Strains not inhibited by concentrations of penicillin of 25, or more, units per cubic centimeter were considered penicillin-resistant; strains inhibited by 5, or less, units per cubic centimeter were considered penicillin-sensitive.

bacilli 100 per cent resistant. No study of the inhibitory power of any of the organisms was undertaken although the experience with the four *B. proteus* strains quoted in the previous section suggests that this might have been interesting.

Approximately 30 per cent of the bacterial strains recovered on the day of injury by swab culture were found to be penicillin-resistant (Chart 6). This 30 per cent was made up of one-half of the diphtheroids and *subtilis*, all of the gram-negative bacilli and 20 per cent of the gram-positive organisms, including streptococci, staphylococci and *Clostridia*. During the course of penicillin therapy, after an increase of penicillin-sensitive strains in the first seven days, there was a progressive disappearance until the 42nd day when

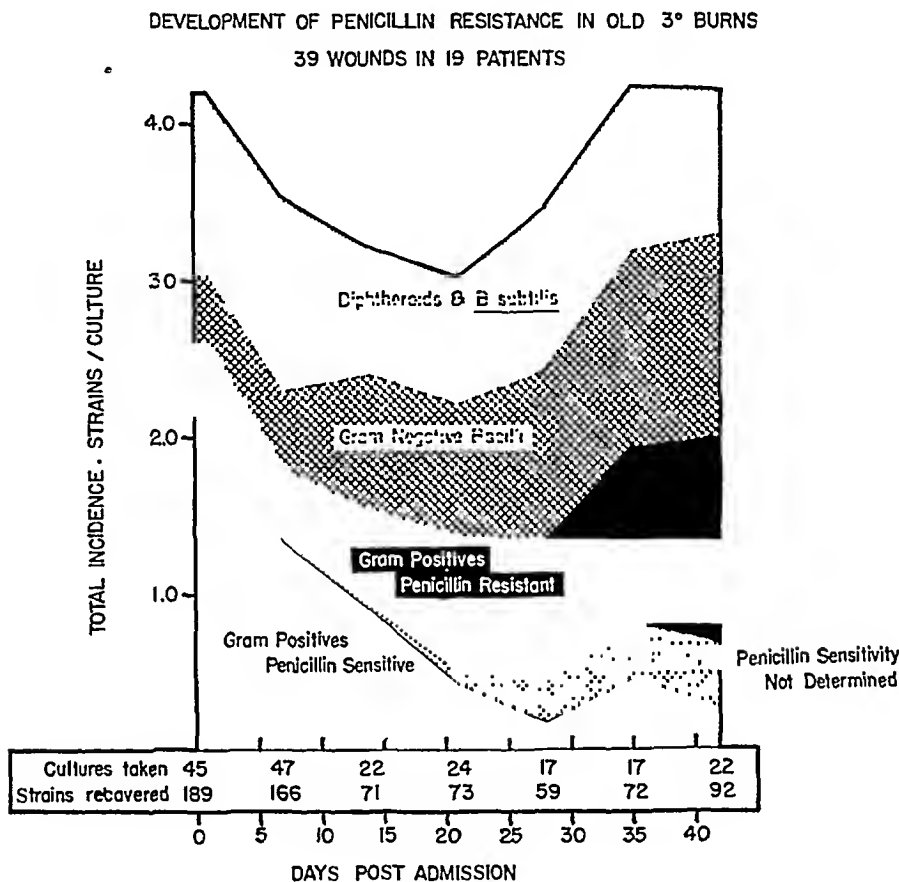


CHART 7

CHART 7.—The Occurrence of Penicillin Resistance in the Flora of Full-thickness Burn Wounds of Patients whose Hospital Admission and Penicillin Therapy were Delayed: Thirty-nine wounds of 19 patients (cf. Chart 2 of Part I) were followed from the day of admission throughout a course of penicillin therapy. Penicillin resistance of the flora was ganged in this group of patients as described in the legend of Chart 6.

the minimum number was reached. During the first seven days there was also an increase in number of resistant gram-positive organisms. After the 7th day, as the sensitive strains disappeared they were replaced by resistant strains in approximately the same proportion. By the 14th day after injury the number of resistant gram-positive strains was quadrupled, and by the 21st day there was only half the original number of gram-positive sensitive strains left. By the 42nd day only 10 per cent of all the gram-positive strains re-

covered were sensitive. In addition to these changes in the gram-positive flora, in the 42 days there had been an eleven-fold increase in the gram-negative strains. Thus, in contrast to the day of injury, when 70 per cent of all of the strains had been sensitive, on the 42nd day not more than 19 per cent were sensitive *in vitro* to penicillin.

The initial occurrence and subsequent development of resistance to penicillin was also studied in the bacteria recovered from the wounds of those patients with full-thickness burn wounds in whom the onset of penicillin therapy was delayed. The gram-positive flora of the 39 wounds of the 19 patients was studied (Chart 7; cf. Chart 2 of Part I).

The trends of decreasing sensitivity and increasing resistance are the same as in those wounds of the patients in whom penicillin was started on the day of injury. The minimum number of sensitive strains is reached earlier, however, at the 28th instead of the 42nd day.

CONCLUSIONS

The progressive increase in numbers of bacteria which are resistant to penicillin and which normally are predominantly sensitive, the concomitant decline in numbers of penicillin-sensitive bacteria and the early overgrowth of bacteria commonly inhibitory of penicillin action in the full-thickness burn wounds of patients receiving penicillin therapy, suggest that the most effective therapeutic period of the drug is sharply limited to the first three weeks. By the 5th week of penicillin therapy the wound is a quagmire of resistant and inhibiting bacterial organisms over which penicillin exerts but little control. Though both drug resistance and inhibition are measured *in vitro*, the parallelism of the observed resistance to, and inhibition of, penicillin by the bacteria recovered from the burn wound and the clinical impression of the limited effectiveness of penicillin in controlling infection in the later weeks of therapy indicate that the tests are significant.

REFERENCES

- ¹ Janeway, Charles A.: Medical Progress: The Sulfonamides: I. Their Mode of Action and Pharmacology. *New England J. Med.*, 227, 989, 1942.
- ² Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit Royal Infirmary, Glasgow, 1942-43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.
- ³ Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin. *Lancet*, 2, 177, 1941.
- ⁴ Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army. *J. A. M. A.*, 123, 1007, 1943.
- ⁵ Abraham, E. P., and Chain, E.: An Enzyme from Bacteria Able to Destroy Penicillin. *Nature*, London, 146, 837, 1940.

(Continue with Part III)

PART III

THE INCIDENCE, VIRULENCE AND RESISTANCE TO PENICILLIN OF THE STAPHYLOCOCCUS IN BURN WOUNDS OF PATIENTS TREATED WITH PENICILLIN OR SULFONAMIDES

THE SIGNIFICANCE OF STAPHYLOCOCCAL IMMUNITY TO THE HEALING OF THE WOUNDS INFECTED WITH THE STAPHYLOCOCCUS

THE POSSIBLY injurious rôle of the staphylococcus in burn wounds has received but scant attention, overshadowed, as it has been, by the flamboyant infection of the streptococcus. With the exception of the tetanus organism, known in a burn wound to give rise occasionally to clinical tetanus, students of infection in burns, traditionally, have been engrossed with the streptococcus. The vital dyes (gentian violet, brilliant green and acriflavine) were introduced by Aldrich,¹ with the objective of controlling the streptococcus. Investigating the effect of the sulfonamides in burns during 1942 and 1943, Colebrook, and his collaborators,² although recounting the presence of the staphylococcus and other organisms, have continued to center their thoughts on the streptococcus. They state: "Staphylococci have given rise to comparatively little acute or serious sepsis, and their influence upon the rate of healing in burns has been much less evident than that of hemolytic streptococci. Unlike the streptococci, too, they have seldom, if ever, been responsible for the failure of grafting operations."

The advent of the sulfonamides, the first relatively nontoxic agent achieving control over the streptococcus, and recent knowledge of the virulence and immunologic reactions of the staphylococci have set the stage for the study of the staphylococcal infection of burn wounds. Lyons,³ in his bacteriologic study of the nine victims of the Cocoanut Grove disaster with full-thickness burns, who were treated with sulfadiazine, found a singular discrepancy in the incidence in the wounds of the streptococci and that of the staphylococci. The *beta* streptococcus was recovered from 30 per cent, or less, of the wounds and had disappeared by the 6th week. The *alpha* streptococcus, present in the 1st week in 60 per cent of the wounds, had disappeared by the 5th week. The *gamma* type was recovered even less often than the *beta*. The staphylococcus, found in every wound, persisted in the virulent form in more than 80 per cent of the wounds throughout the nine weeks of observation. Such a disparity in incidence between the streptococcus and staphylococcus, presumably due to the suppression of the streptococcus by the sulfadiazine, offered a means of judging the destructiveness of the staphylococcus in the wounds of patients to be treated with sulfadiazine. The disparity also offered the control needed to evaluate the effectiveness of penicillin against both streptococcus and staphylococcus.

Also, indicating a more extended study of the staphylococcus in burn wounds, was the recent recognition of the varying pathogenicity of its types and of an immunologic response to its presence. As the result of experience

with surgical infections other than burns; such as the carbuncle, in which the staphylococcus was the sole organism recovered, it was generally agreed⁴⁻⁹ that the clinical virulence of the infection varied with the metabolic type of the staphylococcus. The yellow staphylococcus, *Staph. aureus*, is more virulent than the white, *Staph. albus*; the property of coagulating human plasma protein also denotes greater virulence. Lyons¹⁰ has reported the presence in the blood serum of rabbits injected with heat-killed staphylococci of agglutinins specific for the strain of staphylococcus. By observing the color and coagulating property of the staphylococci found, by search for specific agglutinins and by quantitation of certain nonspecific globulins in the blood serum of the burned patients, it was believed objective data could be obtained regarding the virulence of the infection and the degree of immune response.

METHODS

In addition to the bacteriologic methods recounted in the first two parts and the usual chemical methods for estimating plasma protein, the following methods have been used:

The euglobulin and pseudoglobulin levels of the blood serum were determined by the sodium sulfate protein fractionation method of Howe.¹¹

Specific agglutinins to the staphylococcus recovered from the wound were tested for in the blood serum of the patient by the macroscopic slide-agglutination technic of Lyons.¹⁰

Autogenous staphylococcal vaccine was prepared according to Lyons.¹⁰

OBSERVATIONS

Incidence.—In every full-thickness burn wound the presence of a staphylococcus is to be expected. From each culture taken on the day of injury, 1.1 strains of staphylococci were recovered from the wounds of the patients subsequently treated with penicillin (Chart 9), and 1.2 strains from those of the patients subsequently treated with sulfadiazine (Chart 8).^{*} As pointed out in the first part of this study on bacteriology, during the course of systemic therapy with penicillin the over-all incidence of the staphylococcus in the full-thickness burn wound slowly decreased, while under sulfadiazine there was no change. When the individual wounds are examined, approximately one-third of the wounds under either drug lost their staphylococci before healing had taken place. Of the 46 wounds in patients treated with sulfadiazine, 33 per cent lost their staphylococci. Of the 80 wounds in patients receiving penicillin, 37 per cent lost theirs. This apparent discrepancy with the over-all incidence is explained by the fact that certain patients under

* A slightly higher incidence of the staphylococcus in the 13 cultures made by means of débrided tissue in the cases subsequently treated by sulfonamides might appear to be due to the method of culturing. In the second-degree burns, however, the different methods of culturing yielded identical numbers of staphylococcal strains per culture (Charts 3 and 4 of Part I. The slight difference in the full-thickness burn wound is probably not statistically significant since but 13 cultures were taken in the cases subsequently treated by sulfonamides.

sulfadiazine having multiple wounds lost all staphylococci, whereas other patients acquired two, and even three, different staphylococci per wound, and lost none.

A comparable disappearance of staphylococci from wounds of patients

STAPHYLOCOCCAL VIRULENCE - SYSTEMIC SULFONAMIDES - 3° BURNS

46 WOUNDS IN 25 PATIENTS

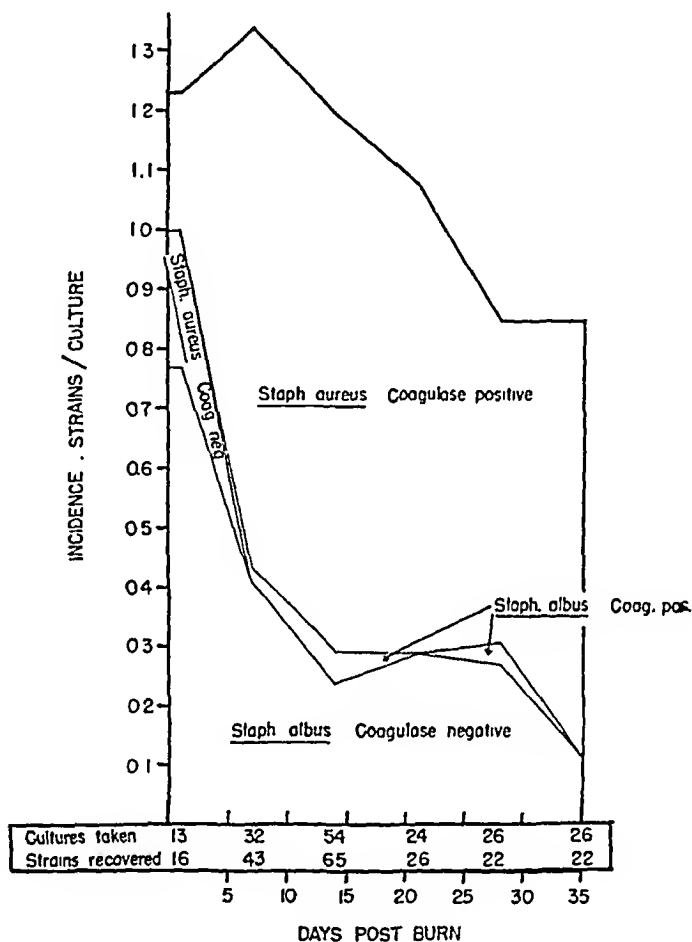


CHART 8

CHART 8.—The Incidence and Virulence of the Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Sulfonamide Therapy: The staphylococci isolated from 46 wounds of 25 patients (cf. Chart 3 of Part I) were tested for chromogenesis and the power to coagulate human plasma protein. (Hemolysis was noted but is not recorded.) Virulence was graded on the basis of these two attributes; thus, the *Staph. aureus*, coagulase-positive, is fully virulent, the *Staph. albus*, coagulase-negative, avirulent.

under no chemotherapy was observed in the few patients available for study during the course of these observations who did not receive one, or another, chemotherapeutic agent. No common factor in the condition of the wounds

of the groups of patients, such as the presence of slough or the local treatment applied, were discerned which could account for the disappearance of the staphylococci.

Virulence.—The number and proportion of virulent strains of the staphylococci increased in full-thickness burn wounds with the passage of time under either sulfadiazine or penicillin therapy. Of the staphylococci recovered on the day of injury 75 per cent were of the least virulent form, *Staph. albus*, coagulase-negative, and but 15 per cent of the fully virulent, *Staph. aureus*, coagulase-positive. The two intermediary groups made up the remaining 10 per cent.

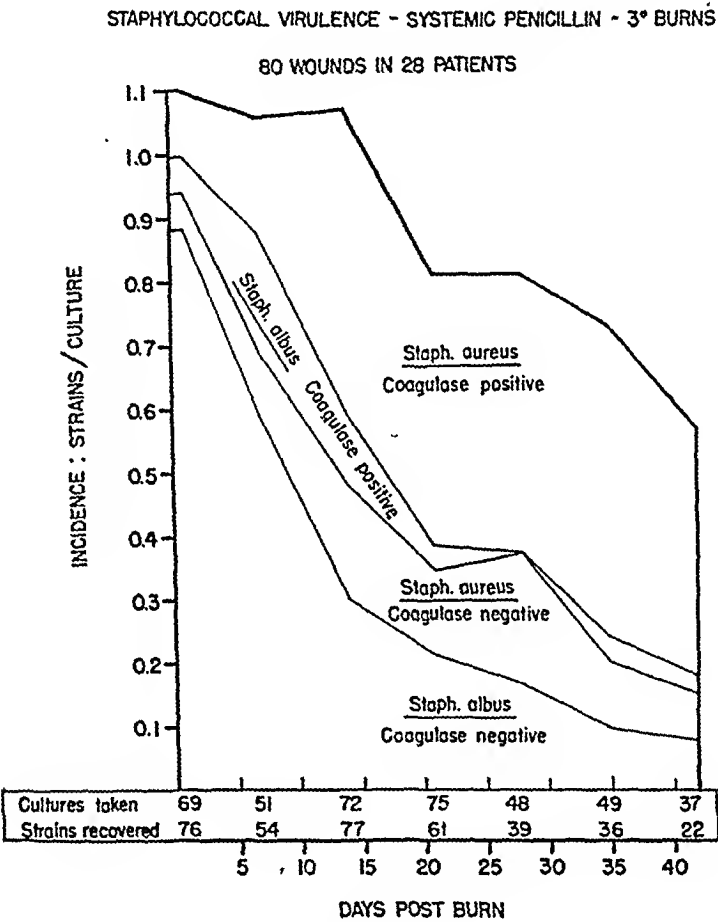


CHART 9

CHART 9.—The Incidence and Virulence of the Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The staphylococci isolated from 80 wounds of 28 patients (cf. Charts 1 and 6 of Parts I and II) were tested for chromogenesis and the power to coagulate plasma and the virulence graded as recounted in legend of Chart 8.

During the course of the first six weeks there was a progressive loss of the avirulent and a steady increase of the virulent forms, until by the 6th week the relation of “*albus*” to “*aureus*” was reversed. At this time, in the penicillin-treated cases the “*albus*,” coagulase-negative, accounted for less than 20 per cent of the strains recovered, and the “*aureus*” for 70 per cent;

in the sulfadiazine-treated cases, 85 per cent of the staphylococci were of the *aureus* form. Even when the decrease in number of total staphylococcal strains under penicillin is taken into account, there was, after six weeks of therapy with either drug, a greater number of virulent strains recoverable per culture which were fully virulent than there had been on the day of injury.

DEVELOPMENT OF PENICILLIN RESISTANCE IN STAPHYLOCOCCI - 3° BURNS

80 WOUNDS IN 28 PATIENTS

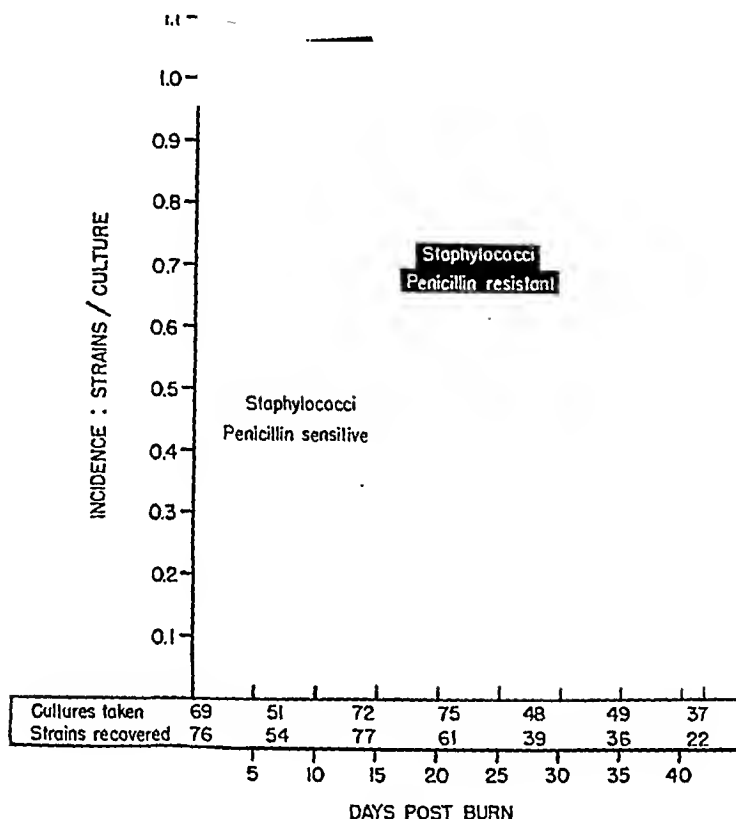


CHART 10

CHART 10.—The Penicillin Resistance of the Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The staphylococci were isolated from 80 wounds of 28 patients (same group as in Chart 9; cf. Charts 1 and 6 of Parts I and II).

The *Staph. aureus*, coagulase-negative, and *Staph. albus*, coagulase-positive, the intermediary types, at any one time made up but a small proportion of the total staphylococcal strains; their number was almost negligible during the course of sulfonamide therapy, while their slightly greater incidence under penicillin is probably statistically significant.

Penicillin Resistance.—Even more striking than the changes in virulence of the staphylococcus recovered from full-thickness burn wounds, with the passage of time, is the development in these organisms of penicillin resistance. In the burn patients subsequently treated with penicillin but 14 per cent of the

BACTERIOLOGY OF BURN WOUNDS

strains of staphylococci were resistant on the day of injury and before onset of therapy. At the end of six weeks of penicillin treatment more than 90 per cent of the staphylococci recovered were resistant to the drug (Chart 10). All four types of the staphylococci developed resistance, but, apparently, not quite to the same degree (Chart 11). The fully virulent types by the 6th week were all resistant. Only the most avirulent form, *Staph. albus*, coagulase-negative, had

STAPHYLOCOCCAL VIRULENCE AND PENICILLIN RESISTANCE - 3° BURNS
80 WOUNDS IN 28 PATIENTS

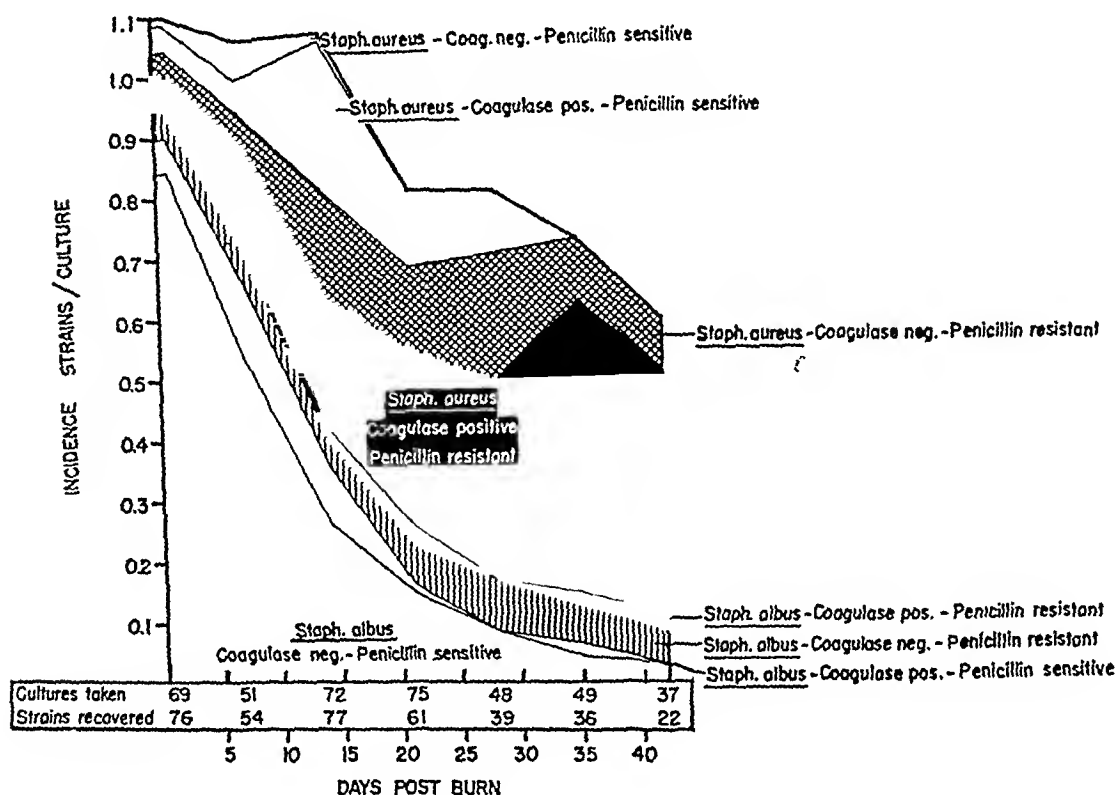


CHART II

CHART II.—The Virulence and Penicillin Resistance of Staphylococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: This is a composite of Charts 8 and 9.

a significant number of penicillin-sensitive organisms during the 5th and 6th weeks of treatment.

Evidence was obtained of two types of acquired resistance to penicillin. The *in vivo*-acquired resistance may be permanent. The burn wound of one patient (Case 188), and the donor site of another (Case 137), both of which were infected originally with a penicillin-sensitive staphylococcus, during the course of penicillin therapy, yielded a resistant organism in place of the sensitive one. After two and 15 weeks of therapy, no further penicillin was administered. Two and one-half and three months after cessation, the staphylococcus recovered from each was still resistant. From the burn wounds of a third patient (Case 168) a penicillin-resistant staphylococcus was recovered three months after cessation of therapy. It is possible in this 3rd

patient that the staphylococcus was resistant before onset of therapy, since she had been treated with penicillin in another hospital before coming here, and no culture had been taken prior to onset of the therapy. The staphylococcus recovered from all three patients was of the fully-virulent type.

The *in vitro*-acquired resistance, which we have succeeded in producing, on the other hand, has proved transient. Penicillin resistance was induced

Postulated Staphylococcal Conversion under Penicillin

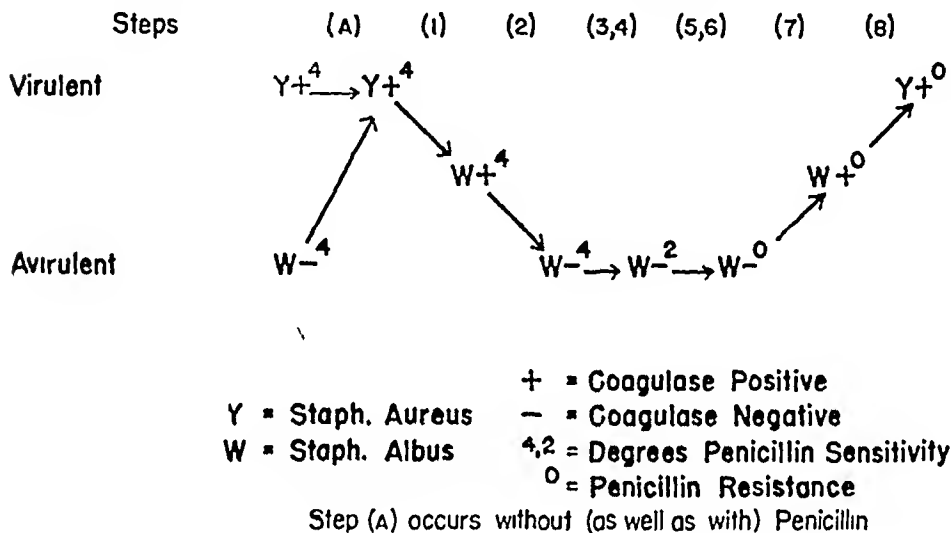


CHART 12

CHART 12.—Postulated Metabolic Mutation of the Staphylococci in the Wounds of Patients Receiving Penicillin Therapy: The frequently observed disappearance of avirulent forms of staphylococci and the appearance of virulent forms in the initial days after injury in patients receiving no chemotherapy or sulfadiazine has suggested a mutation from avirulent to virulent form. A similar change has been noted in the staphylococci recovered from patients treated with penicillin. During the succeeding two weeks of penicillin therapy avirulent forms are again found; such a reappearance has not been encountered in sulfonamide-treated patients or in those receiving no chemotherapy. After the 3rd week of penicillin therapy, when penicillin-resistant strains predominate, virtually all strains recovered are fully virulent. It is postulated that an initial effect of penicillin on staphylococci is a reduction of virulence but that if the staphylococcus survives by developing resistance, full virulence is regained.

in sensitive staphylococci by repeated cultures in media containing increasing concentrations of penicillin. This induced resistance was quickly dissipated by culturing the organisms in penicillin-free media. Only the *Staph. aureus*, coagulase-positive type, was used in these experiments. Spink, *et al.*,¹² have reported comparable findings.

Mutation Theory.—The gradual replacement of the avirulent by the virulent form of the staphylococcus in all burn wounds (Charts 8 and 9) and the frequency with which a change in form has been seen in wounds in which a single staphylococcal strain has been recovered at any one time, point strongly to a mutation of the staphylococcus. Such a mutation from the *Staph. albus*

to *Staph. aureus*, and from coagulase-negative to coagulase-positive has been previously postulated.¹³⁻¹⁵ With the advent of penicillin, evidence has been obtained which carries the concept of the mutation two steps further (Chart 12). The first change of the penicillin-sensitive avirulent white staphylococcus is to a virulent yellow staphylococcus, still penicillin-sensitive. This step is the previously postulated mutation and, apparently, takes place whether the patient is on penicillin or not. In the patients under systemic penicillin therapy, the next change appears to be a reversion to a white form, with loss of coagulating power but still sensitive to penicillin. If the organism does not disappear and chemotherapy is continued, resistance to the drug develops. When the resistance is fully developed there is a second and final reversion to the virulent form.

Proteolysis.—During the course of penicillin therapy the wounds of nine of the patients with full-thickness burns developed a superficial dissolution which we had never previously seen and which was associated with a penicillin-resistant *Staph. aureus* and a *B. proteus*. The wound is characteristic in appearance, stubborn in therapy, and has been termed "proteolytic" because of its salient character. Such proteolytic wounds have not been encountered until after three weeks of penicillin therapy. There is a superficial liquefaction of epidermis and derma unaccompanied by any deep or subcutaneous inflammatory reaction. The margins of the wound, or of grafts previously placed upon the wound, melt away, leaving cadaveric-appearing, uninflamed yellow fat. The veins of the subcutaneous plexus may lie exposed on the surface of the fat, apparently intact, giving the wound its cadaveric look. There is little bleeding from the wound with change of dressing, and no granulations or fibrous tissue proliferation; little edema is visible. The wounds may lie, weeks long, in such an inactive state. After final epithelial closure, a late, and prolonged, deep inflammatory process is common with tenderness persisting as long as six months, and eventual profuse keloid formation.

In all of the proteolytic wounds of the nine patients, a penicillin-resistant *Staph. aureus* and a *B. proteus* was recovered during the proteolytic phase. This same combination of organisms has been encountered in nine of the wounds of other patients under penicillin therapy, without any evidence of proteolysis. Although there were no other organisms common to all the proteolytic wounds, an *alpha* streptococcus was found in several, and clostridial organisms were found in a few.

The late inflammatory reaction occurred in five of the seven patients in whom a proper follow-up was obtained. (Two of the nine patients were obliged to leave this region soon after discharge from the hospital.) One of the two patients not developing the late inflammation was injected with autogenous staphylococcal vaccine in an effort to prevent it (Case 168, see below under Immunity). None of the nine patients having wounds with the penicillin-resistant staphylococcus and *B. proteus* combination, but without proteolysis, had a late inflammatory reaction. Cultures were not obtained in the stage of the late inflammatory reaction, but it is believed that the staphy-

lococcus is involved (see below under Immunity). Up until the time of healing both organisms had been consistently present.

Because this type of proteolytic wound had never been observed by us before, and because all of the patients were on penicillin therapy, it is a temptation to ascribe this proteolytic process to the penicillin-resistant staphylococcus.* It is possible, of course, that chance prevented its occurrence in the sulfonamide-treated patients, or that it was not observed, when present, in these or in burn patients seen before the days of chemotherapy.

The wounds have proven stubborn in healing. All methods of local therapy, including gramicidin, have been tried, largely without success. Attempts to find another common factor have proved unsuccessful. Cachexia was present in one patient at onset, but the wound did not heal with improved nutrition. All of the patients received a high vitamin (including 1 Gm. of cevitamic acid a day), high caloric, high protein diet, comparable to that given to other patients. No evidence was obtained of any different pattern of the 17-ketosteroid excretion or creatinuria from those patients without comparable wounds.

That the staphylococcus was implicated, by more than mere presence, is suggested by the fact that eventual healing in the most stubborn of the wounds was achieved only after specific immunity with rise in agglutinin titer was obtained by injections of autogenous staphylococcal vaccine (Case 168, see below under Immunity).

Immunity.—The control of invasive staphylococcal infection and the healing of full-thickness burn wounds infected with the staphylococcus, may involve immune reactions or considerations beyond local surface treatment and specific antibacterial chemotherapy in the form of penicillin. The immune reactions presumably are both specific and nonspecific. They have been encountered during the study of patients with wounds showing the proteolysis of the staphylococcus and *B. proteus*, described in the preceding section, and with invasive staphylococcal infection not controlled by large doses of penicillin. The staphylococcus in both its penicillin-sensitive and resistant forms has been involved. The specific immune reaction measured was the blood serum's agglutinating power of the specific staphylococcus infecting the patient. The nonspecific tests included the blood serum globulin, euglobulin, pseudoglobulins I and II, albumin and total protein. The situation in which immune reactions are believed to be involved are illustrated by the following case reports:

CASE REPORTS

Immunity and the Healing of Proteolysis: Case 168 illustrates spectacular repeated wound healing and wound recession of proteolytic type, with concurrent change in the titer of agglutinins to the staphylococcus. Final healing was achieved, coincidentally, with vaccine therapy and maintenance of a high agglutinin titer.

* This same proteolytic process was incidentally seen at the Hartford Hospital, at the invitation of Dr. Donald Wells, in one of the victims of the circus fire, in the 4th week after injury. This patient had also been on penicillin therapy.

BACTERIOLOGY OF BURN WOUNDS

A 34-year-old housewife was transferred to this hospital 37 days after receiving extensive deep burns when her house burned down. She had been treated with both sulfonamide and penicillin therapy before coming to this hospital. On entry, she ran a high, spiking fever. Extensive full-thickness wounds of both arms, back, and front of the chest showed signs of deep infection. The patient had been on a "slimming" diet before her injury and had managed to lose 25 pounds. She was thin and cachectic on arrival here, but on a high vitamin, high caloric, high protein diet made a rapid weight gain in the first six-weeks' period. She was given a high dosage of penicillin therapy, with slow subsidence in the febrile reaction.

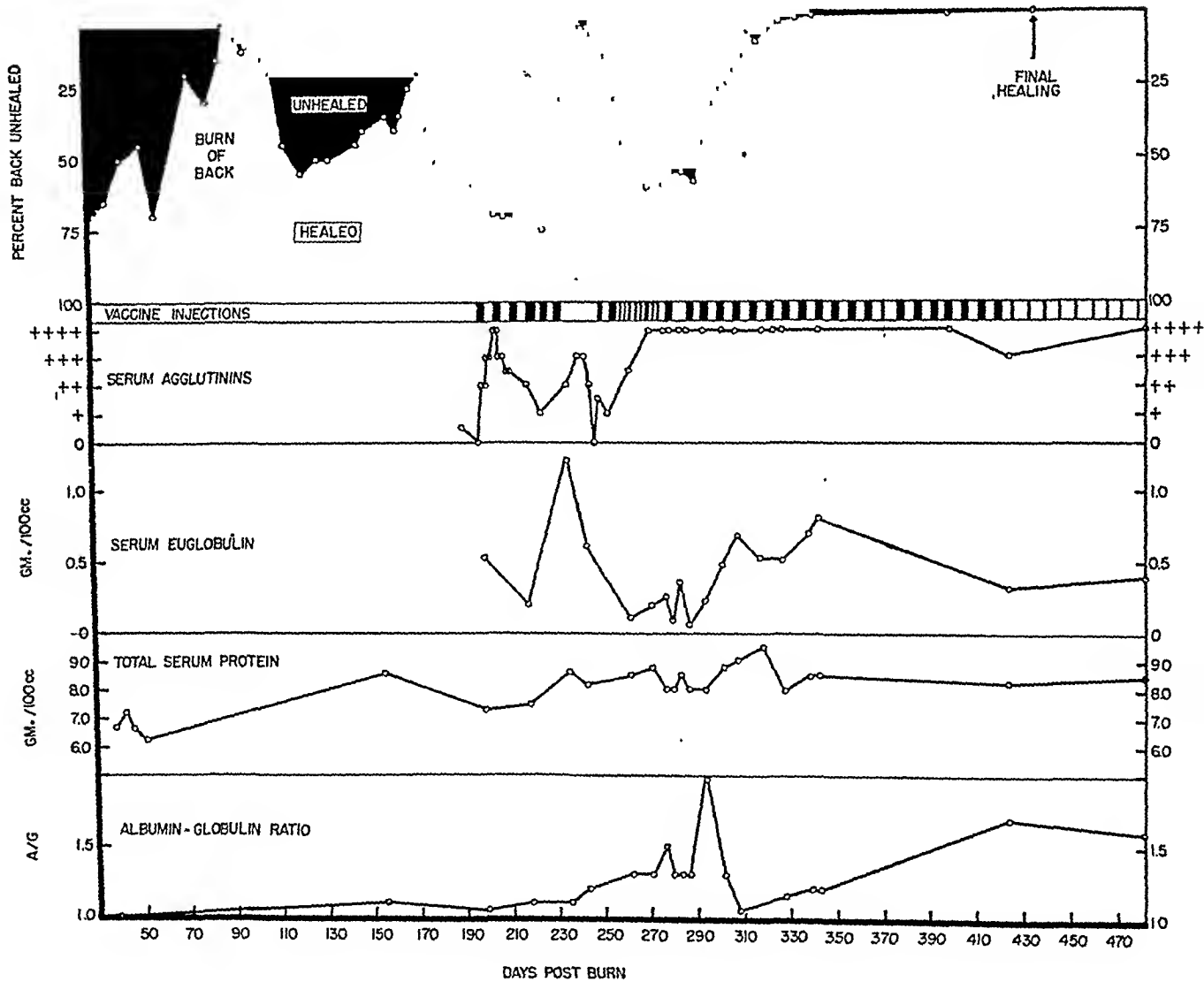


CHART 13

CHART 13.—Case 168: Proteolysis (Wound Dissolution) and Significance of Immunity to Healing: An extensive full-thickness burn wound of the back, 15 per cent of the body surface of a 34-year-old housewife. Thrice nearly healed and thrice dissolved with the fourth and final healing 14 months after injury, coincidentally with a rise in specific immunity. (The patient was transferred to this hospital 36 days after injury; five weeks later, closure of the full-thickness burns of the arms was achieved by grafting.) The back wound was infected with penicillin-resistant *Staph. aureus* and *alpha hemolytic Streptococcus* and *B. proteus*. Penicillin was administered until the 150th day after injury. Autogenous staphylococcus vaccine was started on the 197th day, resumed on the 250th day, and continued until after healing. The last two waves of healing followed rises of staphylococcal agglutinin titer and coincided with rises of serum euglobulin concentration.

The original burn slough was irregularly distributed over the full-thickness burns on entry. During the first four weeks of her stay in this hospital, concomitant with her nutritional improvement, spontaneous epithelization of the wounds started. Five weeks after admission the wounds of both arms and parts of the back were grafted with mosaic grafts. These took well, and there was rapid closure of the wounds of the arms. Subsequent graftings of the wounds of the back and the front of the chest did well initially, the wounds almost closing. On the 8th week after entry, however, the 95th day after injury, the proteolytic process appeared in the wounds of the back and anterior chest and loss of grafts began (Chart 13). By the 120th day after injury virtually all the wounds of the back and anterior chest had reopened. The wounds of the arms remained healed. Various local measures, including gramicidin, were tried in succession. Systemic penicillin was continued throughout. By the 150th day, wound healing was again apparent but the wave of healing was only temporary. By the 190th day proteolytic dissolution of the wounds was once more gaining. Since the patient had achieved an apparently good nutritional state and since the systemic penicillin and the variety of local measures tried had been without effect in ridding the wounds of the proteolytic process or the penicillin-resistant staphylococcus and *B. proteus*, stubborn bacterial inhabitants of the wounds, a trial of staphylococcal vaccine was considered. The agglutinin titer to the persistent *Staph. aureus* proved to be a trace, or 0. The vaccine was, therefore, started on the 197th day, by intramuscular injection, and within a week there was an apparent response, the agglutinin titer rising abruptly to **** (Chart 13). There was no immediate change in the condition of the wound; indeed, the dissolution had progressed and the vaccine was, therefore, continued.

In the 4th week of vaccine therapy, spontaneous closure of the wound had recommenced and proceeded rapidly. The vaccine injections were discontinued on the 235th day, there being in the serum a *** titer of agglutinins and 1.2 Gm. of euglobulin. On the 245th day, proteolysis was again apparent in the wound, and the serum agglutinin titer had fallen to 0. The serum euglobulin level had also declined.

In spite of renewed injections of the vaccine on the 250th day, the proteolysis continued until the open wounds of the back were nearly as extensive as they had been before initiation of the vaccine therapy. Enlargement of the wound ceased simultaneously with the return of the agglutinin titer to ****. Healing of the wound did not recommence, however, for another 20 days, occurring at a time when the euglobulin level once more was rising. This healing phase, the fourth to have occurred, was again from spontaneous regeneration of epithelium; it was prompt and complete. The agglutinin titer remained high throughout the healing period, as did the euglobulin level. During the period when the healing rate was at a maximum the serum total protein level reached the peak of 9.5 Gm. per 100 cc.

The patient was discharged on the 343rd day. Because of the previous tendency of her wounds to dissolve and because of the late inflammatory reaction observed previously in the proteolytic wounds of other patients, the vaccine therapy was continued for another five months. When seen for final follow-up on the 546th day, no inflammatory reaction had appeared. The serum agglutinin titer was ****.

Immunity and Late Inflammation of Proteolysis: Case 210, illustrating subsidence of the late inflammation following the healing of proteolytic wounds coincidentally with a rise in the blood serum of specific agglutinins to the staphylococcus previously recovered from the patient's wounds.

A previously healthy housewife, age 34, received a flame burn of 31 per cent of her body, five-sixths of which was of full-thickness destruction. Although physiologic balance was never stable, a good part of the full-thickness wounds were excised on the 8th day. Small, thin skin grafts were irregularly distributed over the excised areas on the 13th day. The grafts took successfully but before the grafted wounds had closed by spread of epithelium, proteolysis developed in them and in the unexcised sloughing wounds. For two months the grafts retreated. Final closure of the wounds after further grafting was

BACTERIOLOGY OF BURN WOUNDS

achieved by the end of the 4th month. The patient was discharged home on the 128th day after injury.

The patient returned on the 295th day after injury complaining of pain and intense itching of her wounds. Those wounds which had previously harbored the proteolytic process, though firmly epithelized, were swollen, deeply indurated, red and tender, typical of the late inflammation. Fortunately, the virulent, penicillin-resistant staphylococcus recovered from the patient's wounds before healing had been preserved in the laboratory and the patient's blood serum on this day showed a plus two specific agglutinin titer to it. The serum was also found to contain:

Total protein.....	7.9 gm./100 cc.
Euglobulin.....	0.3 gm./100 cc.
Pseudoglobulin I.....	1.7 gm./100 cc.
Pseudoglobulin II.....	0.9 gm./100 cc.
Globulin.....	3.0 gm./100 cc.
Albumin.....	5.0 gm./100 cc.

The patient was not given autogenous staphylococcal vaccine because of the presence of some specific agglutinins. Vitamin C, 2 Gm. per day, was added to her diet.

By the 336th day the late inflammation had subsided. The serum agglutinins were found to have increased to +++. The euglobulin level had more than doubled. The serum protein findings were:

Total protein.....	7.6 gm./100 cc.
Euglobulin.....	0.8 gm./100 cc.
Pseudoglobulin I.....	1.2 gm./100 cc.
Pseudoglobulin II.....	0.8 gm./100 cc.
Globulin.....	2.7 gm./100 cc.
Albumin.....	4.9 gm./100 cc.

The rise in titer of the specific staphylococcal agglutinin and in the level of the euglobulin concomitant with subsidence of the late inflammation suggests that the staphylococcus known previously to have infested the wounds was in part responsible for the inflammation and that specific immunity in the host plays a rôle in the conquering of the organism. Whether the vitamin C aided the host or whether the rise in immunity would not have occurred spontaneously cannot of course be determined from this case.

Immunity and Invasive Infection: Case 218 illustrates the exhaustion of the immune bodies during the phase of advancing cellulitis uncontrolled by penicillin and eventual healing of proteolytic wounds only with return of specific agglutinins. A 54-year-old heavy-set seaman entered the hospital with limited burns of head and face, hands and feet, considered initially to be of incomplete destruction. The wounds were covered; the patient was started on 240,000 units of penicillin intramuscularly per day. Because of advancing cellulitis in the right forearm a blood culture was taken at 48 hours which showed *Clostridia* and *Staph. albus*, coagulase-negative, penicillin-sensitive. Similar organisms were found in the wounds. Because of the continued advance of the cellulitis the penicillin dosage was doubled. The cellulitis was not effectively controlled until the 9th day, after which time it slowly subsided. After three weeks a proteolytic process was noted in the wound of the right hand and what should have been a burn of incomplete destruction turned into one of full-thickness. A similar process was also apparent in the wounds of the feet. Initial grafting tried on these areas was unsuccessful.

The blood serum agglutinins, measured routinely on entry, were +++. On the 2nd and 4th days during the advancing cellulitis they were ++ and +++ but by the 9th day they were 0. The euglobulin titer was also falling during this period. It appeared possible, therefore, that specific antibodies were being exhausted during the period of the advancing infection which was taking place in spite of the large dosage of penicillin. The euglobulin level fell further, reaching 0 during the phase of proteolytic infection.

Because of the proteolysis and absence of detectable antibodies, vaccine therapy was

initiated. The vaccine was injected on three successive days of each week for four weeks before a return and rise in the agglutinins was observed. The reappearance and rise in euglobulins was longer delayed. Wound healing occurred coincidentally with the euglobulin rise, the agglutinins remaining elevated. Although the latent period between onset of vaccine therapy and agglutinin rise was unusually long, bringing up the question of the efficacy of the vaccine, it is to be stressed that healing, as in Case 168, occurred simultaneously with the rise in the euglobulin level and at a time when the agglutinin titer remained high.

Immunity and Invasive Infection: Case 254 was an extensively burned healthy male, age 38, with scattered full-thickness, electric flash-burns who developed, in spite of continued penicillin therapy, an invasive staphylococcus infection in the week following an extensive grafting procedure. Coincidentally with the invasive infection and abscess formation there was a fall in the immune body titer and with its healing there was a rise.

In the first nine days after injury there was a good and immediate immune response to the staphylococci present in the wounds. The agglutinin titer on the 2nd day was 0 but by the 9th had risen to +++. The euglobulin in the same period rose from 0.1 to 0.6 Gm. per 100 cc. The same agglutinin titer was present on the 35th day, though there had been a drop in the euglobulin level to 0.3 Gm. per 100 cc. During these first 35 days there had been prompt healing of the second-degree burns and marginal healing of the full-thickness areas. On the 35th day a multiple grafting operation was performed. Five per cent of the body surface was grafted.

On the 40th day phlebothrombosis was recognized in one leg. Since there were burn wounds covering the usual area of the incision for femoral vein ligation, the phlebothrombosis was treated with intravenous heparin. This was injected into a superficial vein just above the ankle in the leg opposite that showing the signs of phlebothrombosis. This injection was followed 24 hours later by a subcutaneous thrombophlebitis along the calf above the site of the injection and accompanied by a rapidly progressive cellulitis. In order to identify the organism responsible for the cellulitis, on the 46th day an area of necrosis in the cellulitis was aspirated. Culture revealed a virulent *Staph. aureus* identical with that to be found in the wounds; both were penicillin-resistant.

The necrosis in the cellulitis increased and formed a small abscess which was treated successfully with two further aspirations rather than open drainage. The grafts healed satisfactorily during the period of cellulitis and abscess.

It is to be stressed that penicillin, 360,000 units per day intramuscularly, had been continued uninterruptedly throughout the course in the hospital. During the period of abscess formation the agglutinin titer had fallen to plus one on the 46th day. Gradual healing of the abscess occurred coincidentally with the rise in agglutinin titer to +++ on the 60th day, and ++++ on the 70th day. During this period of rise of agglutinin titer, the euglobulin level fell to 0.05 on the 60th day.

CONCLUSIONS

The staphylococcus is destructive and invasive in deep burn wounds of the skin. Its presence is to be anticipated in every wound. In the absence of chemotherapy the number of strains apparently increased, while under systemic sulfadiazine the number was held constant. Under systemic penicillin the number of strains slowly decreased.

The prominence which we have observed the staphylococcus to assume in the infection of the burn wound may conceivably be due to the suppression by chemotherapy of the *beta hemolytic Streptococcus*. The virtual elimination of the rampant streptococcal cellulitis may have destroyed a screen hiding the staphylococcal infection; it is also possible that the *beta* streptococcal infection formally restrained the staphylococcus. The presence of staphylococcal cellu-

litis and bacteremia and the recovery of a greater number of strains of the staphylococcus from the wounds of the burned patients in whom chemotherapy was delayed, however, suggests that staphylococcal infection was present in burn wounds before the days of sulfadiazine or penicillin. It merely failed to attract attention.

Under either sulfadiazine or penicillin the virulence of the staphylococci increased rapidly. On the day of injury three-quarters of the staphylococci were avirulent but by the 6th week this proportion was fully virulent. Even with the gradual reduction in total number of strains under penicillin, there were more fully virulent strains of the staphylococcus in the 6th week than on the day of injury.

Resistance to penicillin developed so rapidly in the staphylococcus and proved of such permanent nature that only within the first three weeks of therapy is the maximum effect of penicillin to be counted upon. On the day of injury but 10 per cent of the staphylococcal strains recovered were penicillin-resistant. By the 6th week of therapy, 90 per cent, including all the fully virulent forms, were resistant.

Proteolysis, or liquefaction of the superficial aspect of a burn wound without deep inflammation, has been encountered in nine patients three weeks, or more, after starting penicillin therapy. The wounds have proved stubborn in healing and after eventual epithelial closure have exhibited later a deep inflammation. The only common factor of these wounds has been the combination of a virulent, penicillin-resistant *Staph. aureus* and a *B. proteus*. Because of the coincidence of the healing of these wounds with a rise in the blood serum of agglutinins specific for the infecting staphylococcus and of the euglobulin level in the patients in whom these measurements were made, it is believed that the staphylococcus is the principal offender and that specific immunity to the staphylococcus is the deciding factor in overcoming the infection. The rôle of the *B. proteus* may be merely that of inhibiting the antistaphylococcal activity of the penicillin, a property which *in vitro* it has been demonstrated to possess.

Other examples of the importance of specific staphylococcal immunity to the control of infection by the staphylococcus in patients receiving penicillin have been found. Invasive infection by the staphylococcus, advancing cellulitis and lymphangitis, and bacteremia, has been repeatedly observed in patients with widespread burn wounds infected with virulent staphylococci and in spite of massive doses of penicillin. In the patients in whom the serum levels of agglutinins and euglobulins have been followed, subsidence of the infection has been accompanied by changes in their levels. The failure of penicillin to achieve control of the infection and the need, therefore, for an immune response by the host may of course have been due to an inadequate concentration of penicillin in spite of the huge dosage. The presence in burn wounds of bacteria inhibiting penicillin and the extensiveness of the infected area may have reduced the drug concentration to an ineffectual level.

Additional evidence for the mutation of staphylococci from one form to

another has been found. An initial action of penicillin appears to transform virulent forms to the avirulent. If the organisms survive, drug resistance develops and reversion to the virulent form follows.

REFERENCES

- ¹ Aldrich, R. H.: Treatment of Burns with a Compound of Aniline Dyes. *New England J. Med.*, 217, 911, 1937.
- ² Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.
- ³ Lyons, Champ: The Management of the Coconut Grove Burns at the Massachusetts General Hospital: Problems of Infection and Chemotherapy. *ANNALS OF SURGERY*, 117, 894, 1943.
- ⁴ Chapman, G. H., Berens, C., Nilson, E. L., and Curcio, L. G.: The Differentiation of Pathogenic Staphylococci from Nonpathogenic Types. *J. Bact.*, 35, 311, 1938.
- ⁵ Blair, J. E.: The Pathogenic Staphylococci. *Bact. Rev.*, 3, 97, 1939.
- ⁶ Fairbrother, R. W.: Coagulase Production as a Criterion for the Classification of the Staphylococci. *J. Path. and Bact.*, 50, 83, 1940.
- ⁷ Goyle, A. N., and Minchin, R. L. H.: A Note on the Biochemical and Serological Classification of the Staphylococci. *Indian J. Med. Res.*, 27, 611, 1940.
- ⁸ Spink, W. W., and Vivino, J. J.: The Coagulase Test for Staphylococci and its Correlation with the Resistance of the Organisms to the Bactericidal Action of Human Blood. *J. Clin. Invest.*, 21, 353, 1942.
- ⁹ Chapman, G. H.: Determination of the Chromogenic Properties of Staphylococci. *J. Bact.*, 45, 405, 1943.
- ¹⁰ Lyons, Champ: Antibacterial Immunity to Staphylococcus Pyogenes. *Brit. J. Exp. Path.*, 18, 411, 1937.
- ¹¹ Howe, Paul E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in Blood. *J. Biol. Chem.*, 49, 93, 1921. *Idem.*: The Determination of Proteins in Blood. A Micro-Method. *Ibid.*: 49, 109, 1921.
- ¹² Spink, W. W., Hall, W. H., and Ferris, V.: Clinical Significance of Staphylococci, with Natural or Acquired Resistance to the Sulfonamides and to Penicillin. *J. A. M. A.*, 128, 555, 1945.
- ¹³ Marziani, R.: Phénomènes de Mutation Présentés par des Staphylocoques, Consécutivement à des Passages par L'Organisme du Cobaye. *Bull. Acad. de Méd., Paris*, 98, 527, 1927.
- ¹⁴ Dudgeon, L. S., and Goadbey, H. K.: Further Observations on the Staphylococci, with Special Reference to their Haemolysins and Variability. *J. Hyg.*, 30, 180, 1930.
- ¹⁵ Pinner, M., and Voldrich, M.: Derivation of Staphylococcus albus, Citreus, and Roseus from Staphylococcus aureus. *J. Inf. Dis.*, 50, 185, 1932.

(Continue with Part IV)

BACTERIOLOGY OF BURN WOUNDS

PART IV

THE INCIDENCE, VIRULENCE AND RESISTANCE TO PENICILLIN OF THE STREPTOCOCCUS IN BURN WOUNDS OF PATIENTS TREATED WITH PENICILLIN OR SULFONAMIDES

IN SPITE of the attention bestowed upon the streptococcus as the most reprehensible contaminating organism of the burn wound, there has been a disparity in the reports of its incidence and disagreement regarding its relation to toxemia in the burned patient. Firor and Aldrich¹ were the first to test the concept that the toxemia of burns is a toxemia of wound infection. From a bacteriologic survey of the flora of burn wounds they reported that although but few contaminants, such as the staphylococcus and *B. coli*, were recovered immediately after injury, by 12 hours after injury the wounds of all the severely burned patients and the large majority of the mildly burned, harbored streptococci. Either the *beta* hemolytic or the *gamma* streptococcus was found. They believed that the subsequent toxemia of the patients was explained by streptococcal sepsis. Such a high streptococcal infestation has not been subsequently reported. Neither the number of patients examined nor the relative frequency of the two types of streptococci were recorded, and it is not known, therefore, whether a representative sample of burned patients was studied.

Cruikshank,² in 1935, also, recorded a high incidence of streptococci in burn wounds. Of 100 burns examined on admission, 11 were found to harbor hemolytic streptococci. Of 32 burns examined between the 3rd and 6th days, 21, or 66 per cent, revealed the hemolytic type of streptococcus. Ten of 490 burned patients developed scarlet fever. Cruikshank made the significant observation that the same kind of streptococcus was to be found in abundance in the air and dust of the wards housing burn patients, but not in those of other wards. He mentioned the presence of the *alpha* type, *Streptococcus viridans*, in some cultures, but he did not record its incidence in detail.

In spite of Cruikshank's collaboratory evidence, Wilson, MacGregor and Stewart,³ in 1938, were loath to accept Firor and Aldrich's concept of early streptococcal toxemia. They found infection in superficial burns to be rare in spite of the presence of hemolytic streptococci and although signs of infection and hemolytic streptococci were found in deep burns they concluded that infection was unusual before the 5th day after injury and, as a rule, not obvious until after the 7th day. They, too, gave no details regarding their bacteriologic studies, mentioning only the hemolytic streptococcus as the usual cause of sepsis.

Seven years later than Cruikshank, and in the same Glasgow wards, Colebrook, and his collaborators,⁴ found a rise in the incidence of the hemolytic streptococcus in the early hours after injury comparable to that reported by Cruikshank, but the actual incidence throughout was slightly lower. This organism was recovered from 4 per cent of 370 burns in the 1st 12 hours, from 23 per cent of 39 in the 2nd 12-hour period, and 42 per cent of 107 burns cultured after 24 hours. Colebrook records strong evidence for contamination subsequent to hospital admission as the source for the increasing number of hemolytic streptococci. Eleven Griffith-types were found among 37 strains recovered from patients cultured on admission, with no one type predominating.

Subsequently, one Griffith-type clearly predominated, nearly all new cases acquiring a strain of this type. Dust and blankets were incriminated as the carriers. Only passing mention is made of a streptococcus other than the hemolytic; two strains of the *gamma* streptococcus were reported as encountered.

In the Contaminated Wound Project of Meleney,^{5, 6} of 1942-43, interest in the streptococcus was also centered in the *beta* hemolytic. No accounting was made of either the *alpha* or *gamma*. It remained for Lyons,⁷ to record the first comprehensive account of the distribution of the *beta* hemolytic, *alpha* and *gamma* streptococci in burns. The flora of the full-thickness wounds of nine victims of the Cocoanut Grove fire were studied in detail subsequent to the 1st five days after injury. Streptococci of all three forms were found, and the *alpha* in the greatest profusion. Sixty per cent of the cultures taken at the end of the 1st week contained an *alpha* strain. *Beta* hemolytic strains were recovered from 30 per cent, or less, of the wounds. *Gamma* strains were found least often. The relatively low incidence of the *beta* strains was ascribable to the sulfadiazine which was being systemically administered to the patients, but the high incidence of the *alpha* type was without precedent and unexplained.

Such were the reports of the incidence of the *beta* hemolytic streptococcus in burn wounds at the time this study was undertaken. With each report, from 1933 to 1943, a lesser incidence of this streptococcus was recorded. In judging the effect of penicillin on the *beta* hemolytic streptococcus in burn wounds, an explanation for this decrease in incidence should be sought. Could it have been due to improvement in measures employed to prevent contamination; to a difference in numbers of this streptococcus in the various cities where the studies were made; or to a difference in season when made or to the recent introduction of the sulfonamides? The sulfonamides had been used both locally and systemically in the therapy of the burned patients reported by Meleney and Lyons.

Such were the meager reports of the occurrence of the *alpha* and *gamma* streptococci in burn wounds. Was Lyons' finding of a prominence of the *alpha* type a chance occurrence peculiar to the night club fire or the result of the sulfadiazine therapy? Are the *alpha* and *gamma* streptococci of burn wounds of any clinical significance?

OBSERVATIONS

The streptococci recovered from the burn wounds were subdivided into the *alpha*, *beta* and *gamma* types. (The *alpha* is the *Streptococcus viridans*, the *beta* is the hemolytic and the *gamma* the nonhemolytic streptococcus). The wounds were of both partial- and full-thickness destruction and of patients treated with either sulfonamides or penicillin. The streptococci recovered from the wounds of patients being treated with penicillin were tested for resistance to penicillin. The coagulase test was also applied to a number of the strains of the *alpha* type recovered from the wounds of the penicillin-treated patients. Search was made for evidence of mutation from one type to another.

Incidence of Types on Day of Injury.—The number and proportion of strains of streptococci per culture recovered on the day of injury differed in the groups of patients treated with either sulfadiazine or penicillin. The major-

ity of the patients treated with sulfadiazine were studied in the two years previous to the introduction of penicillin, and the initial cultures of the wounds of these patients were made from débrided tissue. Seven strains of streptococci were recovered from the 13 cultures of the full-thickness wounds (Chart 14), and 16 strains from the 29 cultures of the partial-thickness wounds (Chart 17), an incidence in each of 55 per cent. The *beta* hemolytic type accounted for three of the strains from the full-thickness, and but one from the partial-thickness wounds. The remaining strains were of the *alpha* type.

The patients treated with penicillin were studied from January, 1944 through December, 1945. The cultures from the wounds of these patients were by the swab technic on the day of injury, as well as later; a larger number of wounds was cultured and a lower incidence of streptococci was found. Streptococci were recovered from 30 per cent of the wounds. No *beta*, 19 *alpha*, and two *gamma* strains were recovered from the wounds of full-thickness, 69 wounds having been cultured (Chart 15). One *beta*, nine *alpha*, and no *gamma* strains were recovered from the 31 wounds of partial-thickness (Chart 18).

Incidence of Types after Day of Injury and without Chemotherapy.—The chance to observe possible changes in the incidence of the streptococci occurring in the absence of chemotherapy, was obtained in the wounds of the 19 patients whose admission to the hospital was delayed and who had received no chemotherapy, local or systemic, prior to entry. Admission of the patients varied from 1 to 30 days after injury, an average of 7.2 days. From the 45 cultures taken on entry and before chemotherapy, 40 strains of streptococci were recovered (Chart 16). Twenty-eight of the strains, or 70 per cent, were of the *alpha* type. Only eight of the strains were of the *beta* and four of the *gamma* type. These patients were studied throughout the same period as the groups receiving penicillin from the day of injury. Some had been treated at home, some in other hospitals prior to entry to this hospital.

Incidence of Types during Sulfadiazine.—In the 1st week after injury in the full-thickness wounds of the patients who were being treated systemically with sulfadiazine, there was an abrupt rise in incidence of the streptococci to a level 60 per cent higher than on the day of injury (Chart 14). During the 2nd and 3rd weeks there was an equally precipitous decline in the incidence to a level approximately half that of the day of injury. Both the rise and fall were due almost entirely to changes in the number of *alpha* strains. After the 3rd week the number of the *alpha* strains remained approximately constant until their final disappearance on the 56th day. The number of *beta* strains remained nearly constant from injury until the 6th week, when there was a decline, with disappearance on the 48th day. On this day, also, all the *gamma* streptococci had disappeared; at any one time but few *gamma* streptococci were recovered.

In the wounds of partial-thickness of the patients who were receiving sulfadiazine there was no increase in incidence of the *alpha* type; there was instead a decline in the 1st two weeks followed by a rise in the 3rd (Chart 17). The *beta* hemolytic type increased slightly in incidence in the 1st two weeks. There was a slow rise in the number of the *gamma* type in the three weeks during which the wounds remained open.

Incidence of Types during Penicillin.—There was a three-fold rise in the

incidence of the streptococci in the full-thickness wounds during the first week of penicillin therapy (Chart 15). The levels reached in the 1st week were maintained in the 2nd. Although there was a decline following this initial rise, it did not occur until the 3rd week, and in contrast to the findings in the sulfadiazine treated patients, it constituted only a partial return to the initial incidence. At the lowest level of this decline, at the end of the 3rd week, the number of strains was still twice as many as on the day of injury. Again in contrast to the sulfonamide cases from the 4th week on the number was again increasing. By the 55th day the number had surpassed the peak of the 1st and 2nd weeks.

STREPTOCOCCI IN 3° BURNS - SYSTEMIC SULFONAMIDES

46 WOUNDS IN 25 PATIENTS

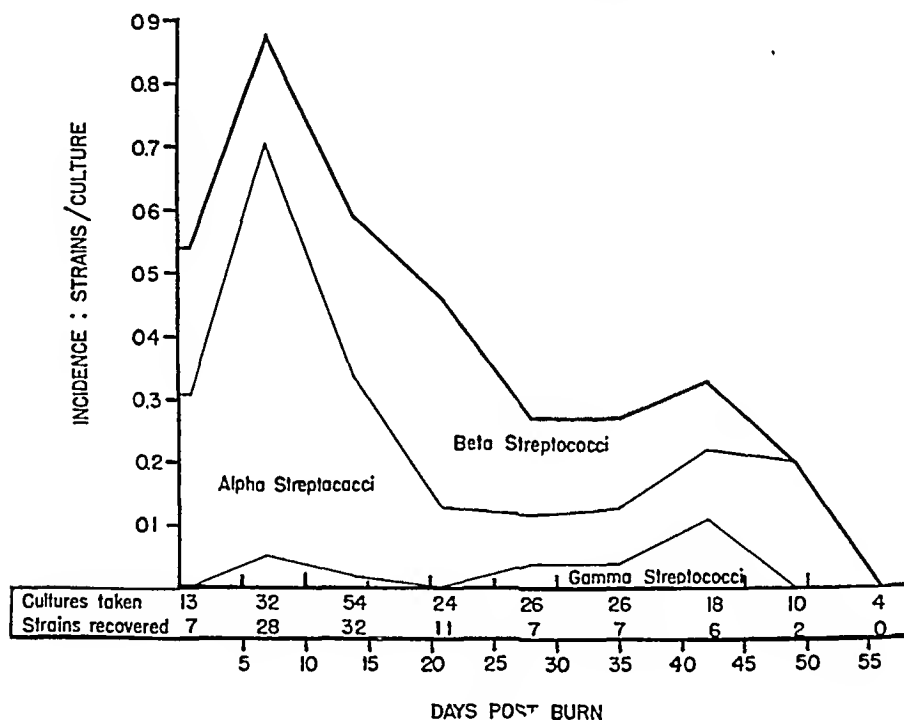


CHART 14

CHART 14.—The Incidence of Streptococci in the Flora of Full-thickness Burn Wounds in Patients Receiving Sulfonamide Therapy: The streptococci isolated from 46 wounds of 25 patients (same patients as in Charts 3 and 8 of Parts I and III) are classified according to the type of hemolysis produced on the blood-agar medium.

A few *beta* strains were recovered in the 1st week. During the succeeding three weeks there was little change in their number and by the end of the 5th week they had virtually disappeared. The number of *beta* strains encountered throughout the period of treatment in these patients was significantly less than in the sulfonamide-treated cases. Although the number of *gamma* strains increased in the 1st week, their number was never large and any fluctuation was not notable. The changes in incidence of the *alpha* type accounted for most of the changes in the over-all incidence of the streptococci. With but 30 per cent of the wounds containing an *alpha* or a *gamma* streptococcus on the day

of injury, by the 57th day 90 per cent of the wounds had an *alpha* streptococcus and a majority of the remaining wounds harbored a *gamma* strain, and a few wounds both. This incidence of the three types of streptococci is again in contrast to the wounds of the sulfonamide-treated cases, which by this time had lost all streptococci.

The changes in incidence of the three types of streptococci following the onset of penicillin therapy in the full-thickness wounds of the patients whose hospital admission and chemotherapy were delayed (Chart 16), were comparable to those encountered following the 2nd week of therapy in the patients

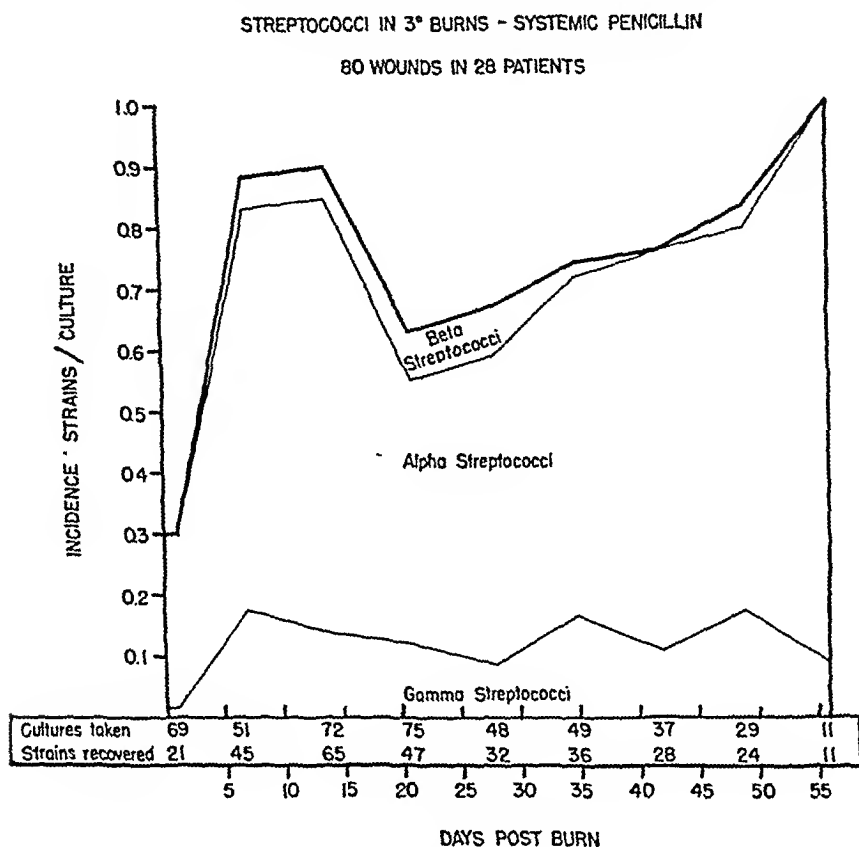


CHART 15

CHART 15.—The Incidence of Streptococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The streptococci isolated from 80 wounds of 28 patients (same patients as in Charts 1, 6, 9 and 10 of Parts I, II and III) are classified according to the type of hemolysis produced.

whose penicillin was started on the day of injury. At entry, there were three times as many streptococci as on the day of injury in the other group of penicillin-treated patients and more than were ever found in the sulfonamide-treated patients. The *beta* strains had virtually disappeared at the end of the 3rd week of therapy. There was an initial decline in the number of the *alpha* strains followed by a continuous rise. In the 6th and 7th weeks of therapy the number of *alpha* streptococci exceeded that at entry. The number of the *gamma* type fluctuated somewhat more than in the previous group.

In the partial-thickness wounds of the patients treated with penicillin the single *beta* strain disappeared in the 1st week, the *alpha* strains remained constant in the 1st two weeks, declining slightly in the 3rd, and the one strain of the *gamma* type encountered was found at the end of the 1st week (Chart 18).

Penicillin Resistance.—The resistance to penicillin of all the streptococci recovered from the wounds of patients being treated systemically with penicillin was measured *in vitro*. No change in the penicillin resistance of the *beta* hemolytic streptococci was found to occur during the course of the penicillin therapy. This finding is in conformity with the earlier report of Rammelkamp and Maxon.⁸ Considerable variation in the resistance of the various strains recovered, however, was observed; some were very sensitive, others

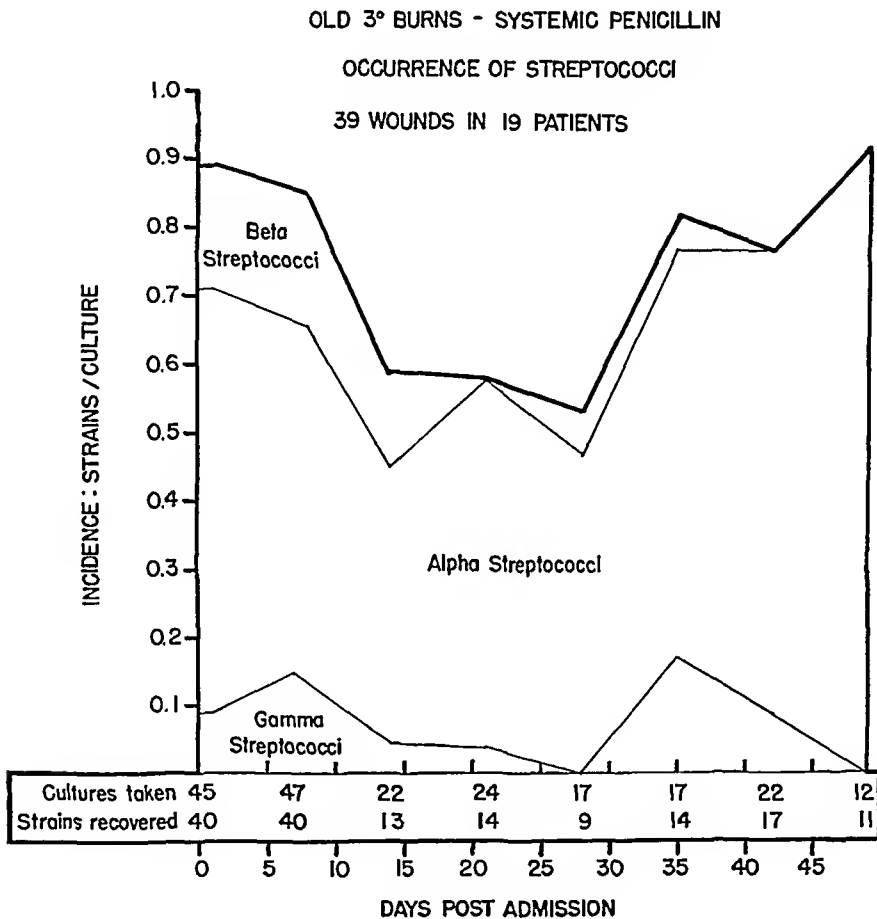


CHART 16

CHART 16.—The Incidence of Streptococci in the Flora of Full-thickness Burn Wounds of Patients Whose Hospitalization and Penicillin Therapy were Delayed: The streptococci isolated from 39 wounds of 19 patients (same patients as in Charts 2 and 7 of Parts I and II) are classified according to the type of hemolysis produced.

resistant. Because of the lack of change in resistance during therapy, the *beta* hemolytic streptococci are omitted from the charts in which the over-all change in resistance is depicted (Charts 19 and 20).

Both the *alpha* and *gamma* streptococci rapidly developed a resistance to penicillin. The resistance was proportionate in the two types to their incidence. In the wounds of the patients whose penicillin therapy started on the day

of injury, only 25 per cent of either organism were resistant on the day of injury, whereas by the 50th day 83 per cent were resistant (Chart 19). In the wounds of the patients whose penicillin therapy was delayed, slightly more, 30 per cent of the *alpha* and *gamma* streptococci, were resistant before onset of therapy (Chart 20). In the 4th week more than 80 per cent were resistant. In this group of patients, the number of sensitive strains increased after the 4th week, but during the same period that of the resistant strains was also increasing. By the 48th day, approximately two-thirds of the *alpha* and *gamma* types were resistant.

Streptococcal Survival beneath the Closed Wound.—Four cases were encountered which indicated that the *beta* hemolytic streptococcus is able to survive the chemotherapy and superficial wound healing. After at least four weeks of continuous sulfonamide or penicillin therapy and complete epithelial closure of the burn wounds, four patients returned to the hospital one to four weeks after discharge with recurrent streptococcal infection deep in the wounds. One patient, who had had a partial-thickness burn, had been given sulfonamide therapy; the other three had had full-thickness burn wounds and had received prolonged penicillin therapy. On readmission, in each case the same strain of *beta* hemolytic streptococcus which had been found in the wounds before healing was recovered by needling the wound. There was prompt subsidence of the invasive inflammation after renewal of the chemotherapy. The cultures taken during the two-week period before healing in the sulfadiazine-treated and two of the penicillin-treated patients had not shown the streptococcus.

Virulence.—The coagulase test, similar to that used on the staphylococci, was applied to a number of the *alpha* streptococci recovered from the wounds of the penicillin-treated patients. A trend of increasing coagulase activity with the development of penicillin resistance was noted. No consistent change in the inflammation of the wound or in the clinical condition of the patient was observed which correlated with this change in coagulase activity. It was, therefore, not ascertained whether this test is an indication of virulence of

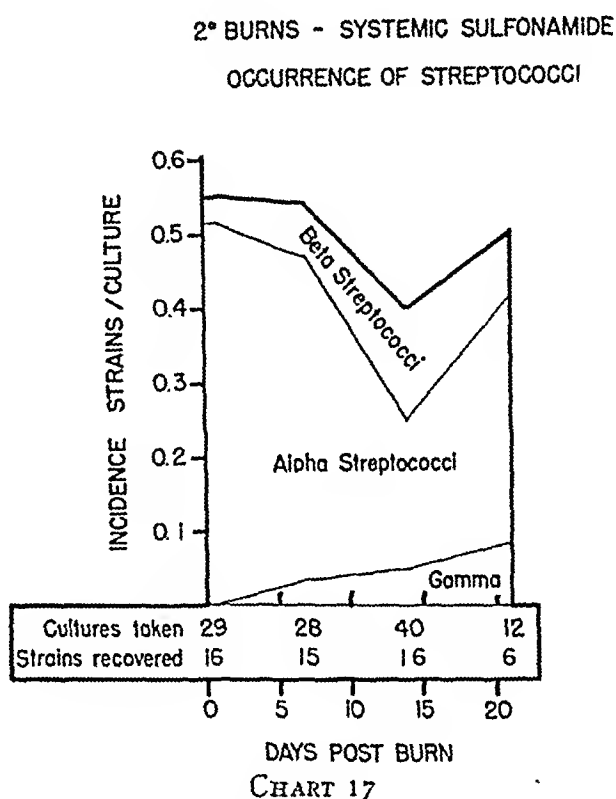


CHART 17.—The Incidence of Streptococci in the Flora of Partial-thickness Burn Wounds of Patients Receiving Sulfonamide Therapy: The streptococci isolated from 58 wounds of 35 patients (same patients as in Chart 4 of Part I) are classified according to the type of hemolysis produced.

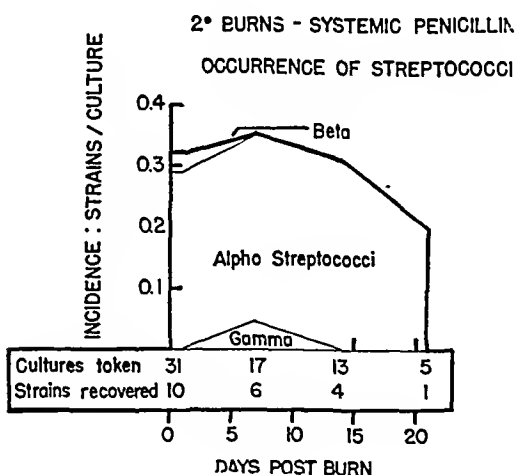


CHART 18

CHART 18.—The Incidence of Streptococci in the Flora of Partial-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The streptococci isolated from 35 wounds of 18 patients (same patients as in Chart 5 of Part I) are classified according to the type of hemolysis produced.

the streptococcus as it is of the staphylococcus.

Mutation. — The rapid disappearance of the *beta* hemolytic streptococcus during penicillin therapy and the simultaneous increase in incidence of the *alpha* and *gamma* forms poses the question of a streptococcal mutation from *beta* to *alpha* or *gamma*, and *gamma* to *alpha*. No consistent sequence of change from one type to another has been noted in wounds from which but one streptococcal strain has been recovered, comparable to that encountered when but one staphylococcal strain was recovered. Evidence for a mutation of the streptococcus *in vivo* in burn wounds is, therefore, lacking.

CONCLUSIONS

It was expected, from the writings of Aldrich, Cruikshank, Colebrook and Meleney, that streptococci would abound in burn wounds but it was not expected that so few of the *beta* hemolytic type, so many of the *alpha* on the day of the injury, and such a profusion of the *alpha* and *gamma* types during the course of penicillin therapy would be found. The incidence of the *beta* hemolytic streptococcus in wounds both on the day of injury and of those of patients whose admission was delayed, was lower than had previously been reported. Could this be ascribed to an attention to prevention of contamination?

Colebrook has emphasized that the *beta* hemolytic streptococcus is not an usual inhabitant of the skin but that the dust of the hospital and ambulance and hospital blanket are likely to be heavily populated with this organism. He deduced that it is from such extraneous sources that burn wounds become contaminated with this type of streptococcus. Inspired by Colebrook, measures to prevent contamination were introduced during the course of this study. Formerly, and during the sulfonamide era, the community was not so burn conscious and not so scrupulous in the emergency handling of burn patients. After the Cocoanut Grove disaster, and at the time when penicillin became available, the physicians of several industries and the staffs of neighboring hospitals were collaborating and forwarding to this hospital their most severely burned patients. Their hospital and ambulance attendants were instructed to use sterile cotton sheets rather than blankets. On arrival at this hospital the patients were promptly placed in an operating room where

BACTERIOLOGY OF BURN WOUNDS

examination and initial care were carried out with precise aseptic technic.

The low incidence of the streptococcus found on the day of injury can probably be ascribed to a new emphasis on prevention of contamination. It is not to be ascribed to a seasonal variation since this study was continuous for two years. The low incidence of the *beta* hemolytic streptococcus found in these same wounds subsequently, during the penicillin therapy, as compared

DEVELOPMENT OF PENICILLIN RESISTANCE OF α AND γ STREPTOCOCCI - 3° BURNS

80 WOUNDS IN 28 PATIENTS

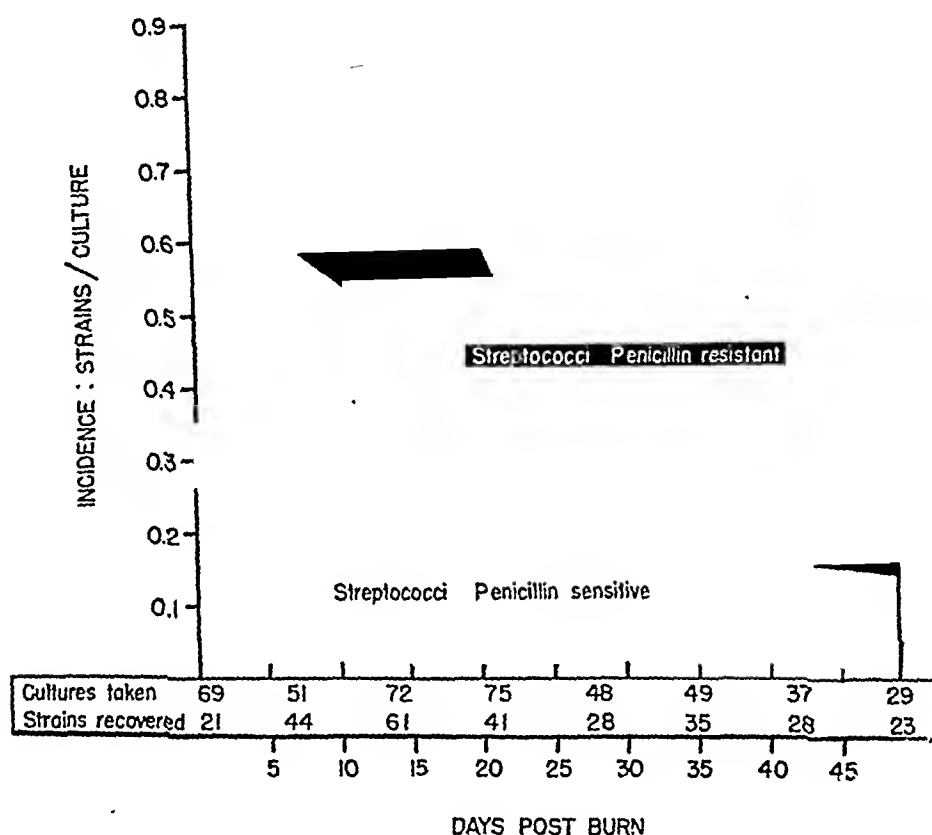


CHART 19

CHART 19.—The Penicillin Resistance of the *Alpha* and *Gamma* Streptococci in the Flora of Full-thickness Burn Wounds of Patients Receiving Penicillin Therapy: The *alpha* and *gamma* streptococci isolated from 80 wounds of 28 patients (cf. Chart 15) were tested for resistance to penicillin. Since the penicillin sensitivity of the *beta* hemolytic streptococcus remained *in vitro* unaltered during the course of penicillin therapy, the strains of this type are omitted from the chart.

with those of the patients treated with sulfadiazine, may be due as much to this emphasis on the prevention of contamination as to the penicillin. Only a few of the patients treated with sulfadiazine were cared for late in the study after penicillin had become available and at a time when the prevention of contamination was being stressed.

More *alpha* streptococci were found in the burn wounds of patients on entry and before chemotherapy was started than had been anticipated and only because the incidence of the *alpha* streptococcus (as well as of the *gamma*) had not been hitherto reported.

The profusion of both the *alpha* and *gamma* types during penicillin therapy was unexpected, particularly since their incidences were so out of proportion to that of the *beta* hemolytic type.

The reason for the profusion and disproportion of incidence of the three types of streptococci during penicillin therapy, however, is explainable when

OLD 3° BURNS - SYSTEMIC PENICILLIN

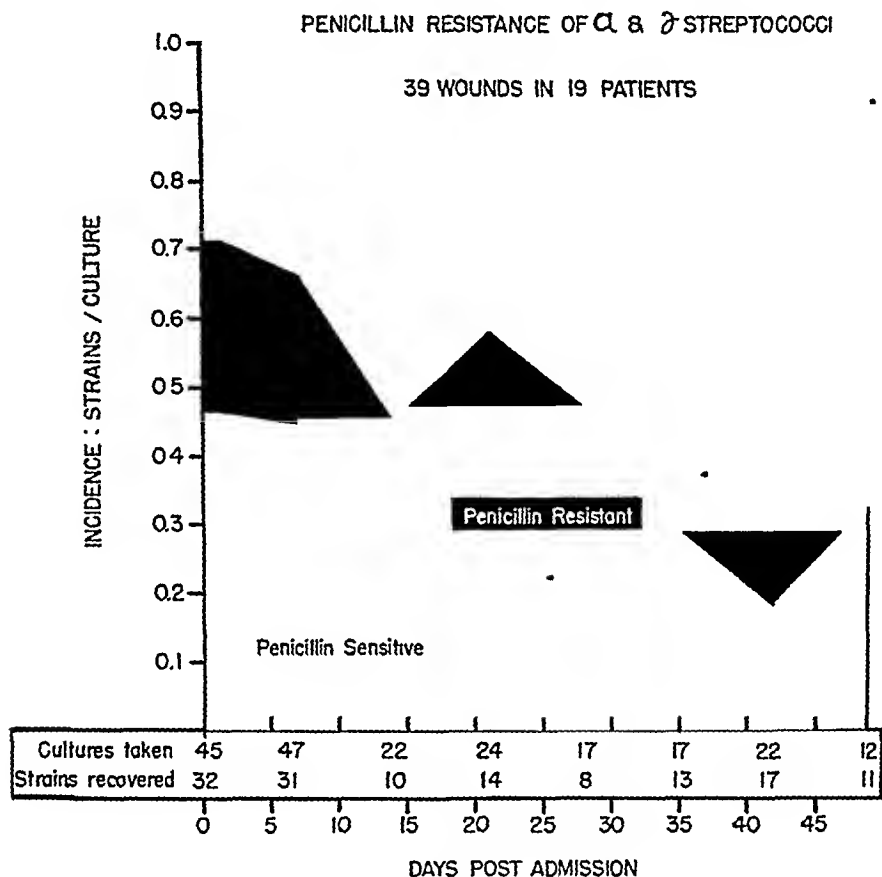


CHART 20

CHART 20.—The Penicillin Resistance of the *Alpha* and *Gamma* Streptococci in the Flora of Full-thickness Burn Wounds of Patients Whose Hospitalization and Penicillin Therapy were Delayed: The *alpha* and *gamma* streptococci isolated from 39 wounds of 19 patients (cf. Chart 16) were tested for sensitivity to penicillin. The *beta* hemolytic streptococci are omitted as from Chart 19.

the *in vitro* studies of the resistance to penicillin are taken into account. The *beta* hemolytic type is unable to alter its metabolism to resist penicillin; it is eliminated.* The *alpha* and *gamma* types, on the other hand, rapidly develop a resistance, survive, multiply and spread.

* It is possible that the slightly greater incidence of the *beta* hemolytic streptococcus in the sulfonamide-treated cases found during the course of therapy was due to its development of resistance to sulfadiazine rather than to the early lapses in preventing contamination. Such drug-fastness has been reported by Colebrook.⁴

Since the *alpha* and *gamma* streptococci were controlled better by sulfadiazine and the *beta* by penicillin, it is conceivable that penicillin and sulfadiazine should be combined in the therapy of patients with deep burns. Only a few of our patients were treated systemically with both of these drugs simultaneously, and too few observations were made for any proof of benefit from such combined therapy. The value of combined therapy depends upon how pernicious the *alpha* and *gamma* organisms are judged to be. The rôle of the *beta* hemolytic streptococcus is unquestioned; its presence in burn wounds is clinically associated with invasive infection, fever and delirium.

The rôle of the *alpha* and *gamma* streptococci in burn wounds is a matter of speculation. Both types are undoubtedly the cause of disease in other body regions. The *alpha* streptococcus recovered from these burn wounds is the same type as that associated with subacute bacterial endocarditis; certain other surgical infections;⁹ and, occasionally, pneumonia in children and young adults.¹⁰ The *gamma* streptococcus is sometimes the micro-aerophilic organism encountered in the undermining ulcer of Meleney and in nonbacillary gangrene. It is also an enterococcus found in the intestinal tract and surmised to be a salient pathogen of mixed infections of the peritoneal cavity. In the burn wound, the *alpha* streptococcus, penicillin-resistant, was commonly, but not always, present in those wounds showing proteolysis. Although no characteristic type of wound inflammation was typical of the presence of either the *alpha* or *gamma* streptococcus, it certainly cannot be concluded, in view of their pathogenicity elsewhere, that they can be dismissed as of no importance in a burn wound. The patients with these organisms in their wounds were sufficiently ill to be hospitalized.

Because of the postulated perniciousness of the *alpha* and *gamma* streptococci in the burn wound it is advised to combine sulfadiazine with penicillin in the therapy of the extensively and deeply burned patient. Since the sulfadiazine is toxic, particularly to the kidney of the dehydrated patient, it is wise to withhold it until an adequate fluid balance is assured.

COMMENT

Infection of the deep burn wound still exists—this study has not eliminated it. It is of mixed bacterial origin, dependent upon the presence of dead tissue, and inadequately controlled by the known chemotherapeutic agents. Its nature is such, and its toxins so mysterious, that there is still a goodly amount of "trial-and-error" involved in the healing of an extensively and deeply burned patient.

Measures designed to avoid bacterial contamination are tried so that there will be fewer bacteria to flourish in the wound.

Measures are chosen in the attempt to starve, remove or kill those bacteria which circumvent the efforts to reduce contamination. The quickest way to starve the bacteria is to remove their favorite food—the slough—by surgical excision. The way to remove the greatest number of bacteria is, also, by excision of the slough, where they have taken refuge.

To kill the bacteria in the wounds which are not excised and not grafted immediately following excision, a combination of penicillin, sulfadiazine and

streptomycin is to be tried. The penicillin, in massive doses, will be the most effective in reducing the number of *beta* hemolytic streptococci and in preventing invasion by the staphylococcus. Its use will be followed by resistant forms of the staphylococcus and of the *alpha* and *gamma* streptococci. The sulfadiazine should be tried in the hope that it will check the profuse growth of the *alpha* and *gamma* streptococci which have become penicillin-resistant. The streptomycin should be tried, also, in the hope that it will abolish the gram-negative bacilli which penicillin allows to flourish and which inhibit the action of the penicillin.

Neutralization of tetanus and clostridial toxins by administration of their respective antitoxins is indicated, particularly in patients with wounds of the buttocks, thighs and legs. (Diphtheria and scarlet fever antitoxins will rarely be needed.)

The patient is not passive as he watches us try to heal his wounds. He, too, can kill bacteria and neutralize their toxins. He will collaborate the better if we help him regain and maintain his physiologic balance.

The problem of the infection of burns will not be solved in the future by repeating a bacteriologic study with the introduction of a new chemotherapeutic agent. This study informs us of the character of the enemy. In the combat, chemotherapy will be a weapon but the replacement of trial-and-error will come only with a better understanding of the toxins of the bacteria and the immune processes of the host.

SUMMARY

A bacteriologic study of the floras of burn wounds has been made, and the effectiveness of penicillin in controlling infection has been judged. The floras of 80 full-thickness wounds of 28 patients treated with penicillin during 1944-45 have been compared with those of 46 similar wounds of 25 patients treated with sulfadiazine during 1942-43. Likewise, and during the respective periods for each drug, the floras of 35 partial-thickness wounds of 18 patients treated with penicillin were compared with those of 58 wounds of 35 patients treated with sulfadiazine. The floras of 39 full-thickness wounds of 19 patients whose admission to the hospital and onset of chemotherapy were delayed and who were subsequently treated with penicillin, were compared with the 80 wounds of the 28 patients whose penicillin therapy was started on the day of injury.

Neither sulfadiazine nor penicillin exerts more than a limited control over the growth of bacteria in the deep burn wound. The staphylococcus was found to be a contaminant of every wound, and the number of its strains to multiply in the absence of chemotherapy. The multiplication did not occur with sulfadiazine therapy and the number of strains recovered slowly decreased during penicillin therapy. Resistance to penicillin developed rapidly, however, and avirulent gave place to virulent forms. The staphylococcus was judged to be a destructive organism in burn wounds. Evidence for the need of immunity to it was obtained.

No *beta* hemolytic streptococci were recovered on the day of injury from

the full-thickness wounds of the patients subsequently treated with penicillin, and very few from the partial-thickness wounds, in contrast to those whose admission was delayed and to the sulfadiazine-treated patients of the previous two years. It is surmised that improved precautions against wound contamination were the cause of this low incidence. There was more prompt elimination of the *beta* hemolytic streptococcus by penicillin than by sulfadiazine from those wounds in which this organism was encountered. This is presumably related to the observed inability of this streptococcus to develop resistance to penicillin.

The *alpha* and *gamma* streptococci slowly disappeared from the wounds of patients treated with sulfadiazine. In the wounds of the penicillin-treated patients, in contrast, these streptococci grew and spread in profusion until by the 8th week, 90 per cent of all the unhealed wounds contained an *alpha* strain and a majority of the remainder, a *gamma* strain, and a few both. These two streptococci were found to develop rapidly a resistance to penicillin.

The number of strains of the gram-negative bacilli increases rapidly in the 2nd week of penicillin therapy. The consistency of this increase with penicillin and its absence in patients receiving sulfadiazine or no chemotherapy, suggests that it is in some manner induced by the penicillin. These organisms were found *in vitro* to inhibit the action of penicillin.

Wounds of the buttocks, thighs and legs showed the greatest contamination with the highest incidence of the *Clostridia* and the *gamma* or fecal type of streptococcus. Wounds of the head and neck revealed the least contamination with no *gamma* streptococci and but few *Clostridia*. The amount of contamination of the wounds of the upper extremities lay midway between the other two body areas. It is suggested that clostridial antitoxin be considered in addition to tetanus antitoxin and prompt excision of slough in the therapy of patients with full-thickness wounds of the lower extremity.

The rapid development of resistance to penicillin by the previously sensitive staphylococci and streptococci and the profusion of penicillin inhibiting and insensitive gram-negative bacilli indicate that the effective period of penicillin therapy is sharply limited to the 1st three weeks. By six weeks after injury the wounds have become a bacterial quagmire.

The infection of burns is a problem of deep burns. The fight against it combines prevention of contamination, starvation of the bacteria by prompt excision of slough, an attack by penicillin, streptomycin and sulfadiazine, and bolstering the immune processes of the host by restoration and maintenance of physiologic balance of the patient.

REFERENCES

- ¹ Aldrich, R. H.: The Rôle of Infection in Burns: The Theory and Treatment with Special Reference to Gentian Violet. New Eng. J. Med., 208, 299, 1933.
- ² Cruickshank, R.: The Bacterial Infection of Burns. J. Path. & Bact., 41, 367, 1935.
- ³ Wilson, W. C., MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds under Modern Methods of Treatment. Brit. J. Surg., 25, 826, 1937-38.

- ⁴ Colebrook, L., *et al.*: Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43). Medical Research Council, Special Report Series No. 249, London: His Majesty's Stationery Office, 1944.
- ⁵ Meleney, F. L.: The Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns. *ANNALS OF SURGERY*, 118, 171, 1943.
- ⁶ Meleney, F. L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft-part Wounds, Compound Fractures, and Burns, with Special Reference to the Sulfonamides. *Surg. Gynec. Obst.*, 80, 263, 1945.
- ⁷ Lyons, Champ: The Management of the Cocoanut Grove Burns at the Massachusetts General Hospital: Problems of Infection and Chemotherapy. *ANNALS OF SURGERY*, 117, 894, 1943.
- ⁸ Rammelkamp, C. H., and Maxon, T.: Resistance of *Staphylococcus aureus* to the Action of Penicillin. *Proc. Soc. Exp. Biol. & Med.*, 51, 386, 1942.
- ⁹ Naffziger, H. C., Warmer, H., Stern, W. E., Fenlon, R., and McCorkle, H. J.: Penicillin in Infections Involving the Central Nervous System and Skull. *J. A. M. A.*, 131, 1183, 1946.
- ¹⁰ Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., Jr., and Horsfall, F. L., Jr.: Studies on Primary Atypical Pneumonia. II. Observations Concerning the Relationship of a Non-Hemolytic *Streptococcus* to the Disease. *J. Clin. Invest.*, 24, 227, 1945.

BRIEF COMMUNICATIONS

EXPERIENCES WITH SYMPATHECTOMY FOR SEQUELAE OF TRENCH FEET

MAJOR A. Krontiris*

ATHENS, GREECE

IN THE ANNALS OF SURGERY, of July, 1945, we read the article by Lt. Col. James Kirtley, Jr., entitled "Experiences with Sympathectomy on Peripheral Lesions." Among the various lesions upon which he applied sympathectomy as a method of treatment, the writer mentions the results he obtained for sequelae of "trench feet."

During the last war, in which Greece had been obliged to engage herself, in the year 1941, against the Italians in Albania in full midwinter, the Greek Army, composed of about 400,000 combatants, was struck, in the form of an epidemic, by "trench feet"; the cases having amounted to 25,000 in number. It is easy to understand that during the following years, when Greece was under German occupation, *i.e.*, 1942-1943-1944, we were compelled to cure a large proportion of these patients for sequelae of "trench feet."

Among the various methods of treatment, we, in some cases, applied sympathectomy, and communicated our results to the Medico-Surgical Society of Athens. As they only partially coincide with the results published by the above mentioned author, and possess the added advantage of having been under observation during a longer period (more than two years), we wish to publish them so that, whoever is interested in that question, might form a more complete opinion on it. Our cases, 27 in number, dealt with patients who showed sequelae of "trench feet," dated from a long period, and exhibited the following physical signs:

- (1) Cyanosis, especially when the feet were dependent.
- (2) Gangrene of toes or ulceration of the skin.
- (3) Trophic changes of the skin.
- (4) Excessive sweating from pearly white, papular lesions on skin, with or without ulceration.
- (5) Neuralgic pains.

Before the operation, the peripheral pulsations were taken with the Pachon manometer. They were always found considerably diminished, either by comparison to the other limb, if it was in a healthy condition, or by comparison to the upper extremities, or to the general pulsations of the lower extremities, in cases where both had been attacked.

We have, also, not omitted to study the temporary beneficial effect in most cases of the injection of novocaine into the sympathetic block.

* Lecturer of Athens University, Director of Surgical Department, 421st Military Hospital, Athens, Greece.

We have employed that very method as one of the preoperative indications of the action of the operation. The results obtained by sympathectomy can be divided into two categories: (1) Immediate results; and (2) delayed results.

Immediate Results.—It has been observed that, a few hours after the operation, the local temperature rises considerably. The pains, strong or slight, as also the numbness from which the patient had been suffering, were lessened and proceeded towards total recovery day-by-day.

In cases of hyperhydrosis which, as known, is one of the most serious complaints of the patients, we have noticed that it disappears on the following day, never to return.

Delayed Results.—These concern chiefly cases of ulcerations. Sympathectomy does not seem to have a great effect upon ulcerations. In summary, the following could be said on that subject:

- (1) That as long as the ulcerations are situated in the lowest part of the leg, they are healed rapidly and permanently.
- (2) If they concern stumps of the feet, not according to type, in the articulation of Lisfranc and Schopart, or if they are placed on the heel, their cure is long and difficult. In the case of a complete cure, the epidermic covering was so thin, that it cracked with the first attempts of the patient to walk.

We do not omit to remark that we have more than once obtained, at a second trial, a good epidermic result with a plastic operation, either through the method of Thiersch, or through the Italian method.

Considering the general rule, according to which plastic operations upon "trench feet" are not always a success, we must attribute the success of the above plastic operations following sympathectomy, to the improvement in the circulation of the feet caused by sympathectomy. In spite of that, one might wonder if, and how much, the sympathectomy causes the healing of those wounds, or whether it is the obligatory rest in bed of the patients, causing the limb to repose in the elevated position in which, as a rule, it is placed. The answer to this question is somewhat difficult.

Without refusing to acknowledge the beneficial effect of sympathectomy in the cure of such ulcerations, we agree more as to the results of rest, for the following reasons: (1) Because we have seen the cure of such ulcerations to take place on medical patients who were simply obliged to stay in bed without undergoing any other treatment; (2) we have had cases of ulcerations on both legs, in which sympathectomy was done on one. In those cases we observed that both limbs were cured in almost the same period of time; and (3) we have also noticed a case in which both feet were ulcerated. The sympathectomy on the right foot did not heal the ulcerations on the left, which were, however, completely cured after the patient had stayed one month in bed.

CONCLUSIONS

The operation of the lumbar block sympathectomy upon "trench feet" may be considered, in general, as a satisfactory operation. Its success being steady, but temporary, as far as pains and the vasometric troubles are concerned, seems doubtful and uncertain for the healing of ulcerations as also in other circulation and neurotrophic troubles.

LIGATURE CARRIER FOR VAGINAL HYSTERECTOMY

ROBERT TAUBER, M.D.

PHILADELPHIA, PA.

ASSOCIATE IN GYNECOLOGY-OBSTETRICS IN THE GRADUATE SCHOOL OF MEDICINE
OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

IN PERFORMING a vaginal hysterectomy most surgeons use a needle and needle-holder for ligating the uterine ligaments, vessels, and adnexa. The needle, however, frequently tears the rubber gloves and pricks the finger. To overcome this accident, pointless needles have been recommended; it is also possible to grasp the needle close to the needle point instead of the needle eye and to use the inverted needle combined with the needle-holder like a ligature carrier.

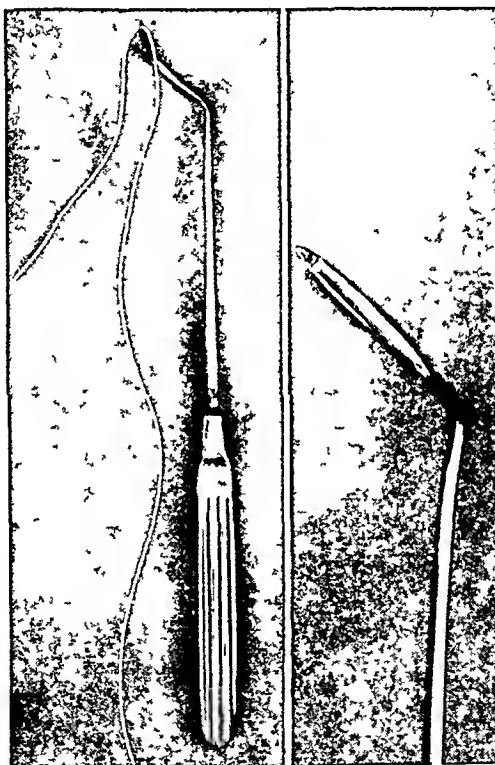


FIG. 1

FIG. 2

FIG. 1.—The portion of the ligature in the concavity of the carrier's head is three times as long as in the convexity.

FIG. 2—The transverse curve close behind the eye permits catching the ligature as soon as it becomes visible.

The use of needle and needle-holder, however, is complicated at times by needle breakage and improper needle fixation. The usual ligature carrier eliminates these inconveniences, but in performing vaginal hysterectomy this carrier has the following disadvantages: (1) The eye is too distant from the needle point and the oval shape of the big eye makes it necessary to pass a long part

of the instrument before the ligature becomes visible; and (2) the usual carrier has a longitudinal groove starting from the eye and running in the axis of the needle. (3) The ligature often lodges in the groove and cannot be grasped easily, furthermore, the groove causes a sharp edge at the eye and spoils the ligature; and (4) the angle between the needle and the handle of the usual carrier is 90 degrees, which makes it very difficult to apply ligatures to both sides of the uterus.

The following modifications are suggested for the ligature-carrier for performance of a vaginal hysterectomy:

1. The angle between the curved needle and the handle is 45 instead of 90 degrees (Fig. 1). This makes it much easier to place the ligatures to either side of the uterus.

2. The eye is circular and small (Fig. 2). The placing of the eye extremely close to the needle point permits catching the ligature immediately after passing the point of the instrument.

3. The edges of the eye are dull in order to avoid damage to the ligature.

4. There is no longitudinal groove following the eye, which hides the ligature. Instead, a transverse groove is placed close behind the eye (Fig. 2), which permits catching the ligature as soon as it becomes visible. A small, blunt, rectangular hook which fits into the transverse groove is very useful for this maneuver. Instead of the hook a toothless forceps can be used.

A small, but important, technical detail should be emphasized for the application of ligatures with a carrier. The eye divides the ligature into two portions (Fig. 1). These portions should not be equal in length, so that only a small portion of the ligature has to be pulled through the eye in order to disengage the ligature from the carrier. This prevents tangling and damaging of the suture material. The portion of the ligature in the concavity of the carrier's head should be three times as long as the portion on the convexity (Fig. 1). Another point is that the hook, or the forceps, which catches the ligature should not pull on it. Holding the instrument still after catching the ligature, the mere retraction of the ligature carrier will disengage the ligature with the least injury to the suture material.

SOLITARY EOSINOPHILIC GRANULOMA OF RIB

CASE REPORT

LT. COL. B. G. P. SHAFIROFF, M.C., AND MAJOR L. SCHEMAN, M.C.

BROOKLYN, N. Y.

EOSINOPHILIC GRANULOMA of bone is claimed to be an acute manifestation of a basic disease process associated with such chronic variants as nonlipoid histiocytosis (Letterer-Siwe disease) and lipogranulomatosis (Schuller-Christian disease¹). It is characterized by single or multiple destructive lesions in the bony skeleton except those of the hands and feet, by a localizing symptomatology and by a well-defined histopathology. The diagnostic importance of this condition and its increasing incidence justify the present case report.

Case Report.—A male, age 31, was transferred to our hospital with the diagnosis: "Other diseases of bone, osteolytic lesion of 6th rib, right posterior axillary line, duration two months, cause undetermined." On admission, the patient complained of pain in the anterior side of the right chest near the sternum at the level of the 6th rib. At rest, the pain was vague and ill-defined but with movement of the right arm, became sharp and lancinating and was referred then to the posterior chest. The past medical history was noncontributory even after the final diagnosis was established. Physical examination was within normal limits except for point tenderness over the 6th rib posteriorly just lateral to the medial border of the scapula when the arm was held in acute adduction.

Laboratory Data.—The Wassermann and Kahn tests were negative. Blood count and differential smear were normal in each of four examinations. Sedimentation time (Wintrobe method) was 11 mm. and 14 mm. for 60 minutes. The hematocrit cell volume averaged 46 per cent. The blood chemistry for phosphorus was 4.2 mg. per cent, for calcium 9 mg. per cent, and for serum phosphatase, 5 per cent. Urinalysis was negative for Bence-Jones protein. Temperature, pulse and respiration while in the hospital were normal.

A variety of roentgenologic studies were made in this case. The initial study revealed an osteolytic lesion, 2 cm. in length, located on the posterior axillary line of the 6th rib, suggestive of malignancy, myeloma or osteomyelitis. Roentgenograms of the entire bony skeleton failed to reveal a similar lesion anywhere else. Roentgenologic studies of the gastro-intestinal tract, the genito-urinary tract and the lungs were negative for a primary malignant tumor in these systems. Follow-up roentgenograms of the involved rib showed it to be a slowly growing, irregularly destructive process which after four weeks of observation began to show evidence of mild periosteal reaction, some areas of bony condensation and, finally, fracture through the site of pathology.

In the differential diagnosis, Ewing's tumor, primary myeloma, osteitis fibrosa cystica, metastatic carcinoma, osteogenic sarcoma, osteomyelitis, syphilis and tuberculosis of the rib were considered. The location of the lesion in the bony shaft, the lack of periosteal reaction, the failure to discover a primary focus of malignant tumor and the laboratory data served to exclude it from the neoplastic group. In a like manner, the usual inflammatory conditions of bone such as osteomyelitis, tuberculosis and syphilis were eliminated. Thus, there remained for diagnosis the more unusual pathologic entities of which only fibrous dysplasia and eosinophilic granuloma of bone merited consideration. The well-being of the patient clinically and the absence of major constitutional manifestations further supported the view in favor of a simple benign lesion.

Five weeks after admission to the hospital, and approximately three months after the onset of symptoms, the involved area of the 6th rib was resected. At operation, a

EOSINOPHILIC GRANULOMA OF RIB

healing pathologic fracture was noted. The rib appeared eroded and filled with a yellow granular tissue. The disease process was localized to the rib. The surrounding tissues, both superficial and deep, were not involved in the pathologic process.

Microscopic sections through the rib showed areas of normal rib and a good deal of new bone formation, resulting in girate patterns. The intertrabecular tissue was



FIG. 1.—Eosinophilic granuloma in rib. The lesion is irregularly destructive with areas of bony condensation along the edges of the process.

loose, fibrillary, highly vascularized and contained a few marrow cells. Nearer to the periphery there were large collections of eosinophils, many of which were mononuclear, while others were polymorphonuclear. Interspersed among the latter arranged in sheets, strands and nests, were large, pale-pink staining cells (histiocytes) with elongated or indented nuclei. *Pathologic Diagnosis:* Eosinophilic granuloma.

Eosinophilic granuloma of bone is rapidly assuming importance as a specific clinical entity. Although originally described as a disease of the very young² it is also found to exist in the adult. Its relationship to virus infection or trauma remains to be determined. The underlying cellular pathology of

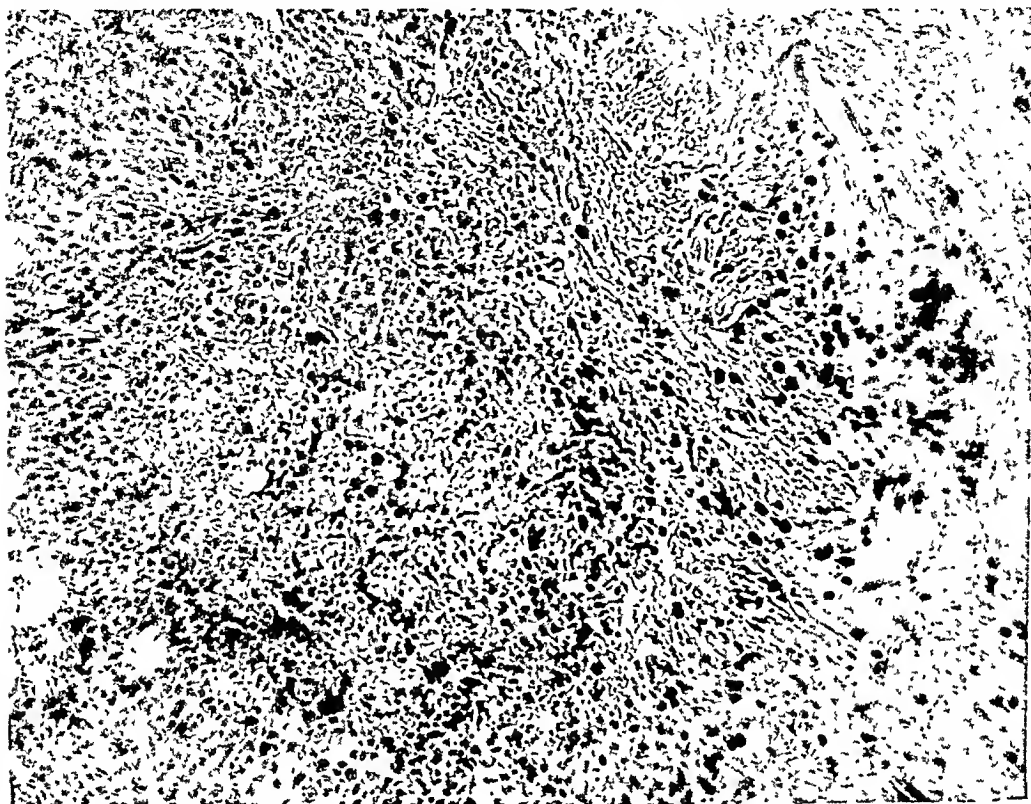


FIG. 2.—Microscopic section from lesion showing concentration of eosinophils with some histiocytes.

histiocytosis and eosinophilic granuloma is also present in nonlipoid histiocytosis and lipogranulomatosis of bone. Hence, the belief that eosinophilic granuloma is an acute variant of the latter two chronic conditions. Treatment is not specific, since this is a self-limiting, spontaneously regressing disease, which is best treated in conformity with general surgical principles.

REFERENCES

- ¹ Jaffe, H. L., and Lichtenstein, L.: Arch. Path., 37, 91, 1945.
- ² Green, W. T., and Farber, S. J.: J. Bone and Joint Surg., 30, 499, 1942.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.

ANNOUNCEMENT



The J. B. Lippincott Company announces with regret the resignation of Dr. Walter Estell Lee as Chairman of the Editorial Board of the ANNALS OF SURGERY. The editors join with the publishers to express their deep appreciation of his keen leadership over the past twelve years. His selective experience and sound surgical judgment have contributed much to making the ANNALS OF SURGERY of increasing value to the practicing surgeon and to the growing number of younger men who are rising into the specialty.

The publishers wish also to announce that at a recent meeting of the Board, Dr. John H. Gibbon, Jr., of Philadelphia, was elected Chairman of the Editorial Board. Dr. Gibbon, who is Professor of Surgery and Director of Surgical Research at Jefferson Medical College, Surgeon to Jefferson Medical College Hospital and the Pennsylvania Hospital, besides being Recorder of the American Surgical Association, brings to this position a wide background and leadership in surgery.

Coincident with this change it is planned that the ANNALS OF SURGERY will broaden its editorial supervision by creating an Advisory Board. Senior men, as they may resign or reach retirement, will be invited to remain in this advisory capacity so that the ANNALS OF SURGERY may continue to benefit from their wisdom and wide experience. As new appointments are made by the publishers as a result of conferences with the senior men and Dr. Gibbon, as Chairman of the Editorial Board, these new men will have the advantage of consulting with this senior body for advice and opinion.

PLEASE NOTE



NEW EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

John H. Gibbon, Jr., M.D.
1025 Walnut Street, Philadelphia 7, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to Dr. Gibbon at the above address.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.



TRANSACTIONS OF THE SOUTHERN SURGICAL ASSOCIATION

MEETING HELD AT HOT SPRINGS, VA.
DECEMBER 10-12, 1946

THE MORTALITY OF SURGICAL DISEASE*

EDWIN P. LEHMAN, M.D., AND WALTER F. BECKER, M.D.
CHARLOTTESVILLE, VA.

FROM THE DEPARTMENT OF SURGERY AND GYNECOLOGY AND THE UNIVERSITY HOSPITAL,
UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE, CHARLOTTESVILLE, VIRGINIA

AS ALL SURGEONS KNOW, in 1946 the patient requiring the attention of a surgeon has a much better chance for recovery than he has ever had before. It may seem presumptuous to present evidence before this body that this is true or to develop figures measuring to what degree it is true. However, there are certain implications arising from the current steady decline in surgical mortality that are frequently ignored or misinterpreted by medical writers, both surgeons and nonsurgeons. The purpose of this paper is to present the curve of annual surgical hospital mortality at the University of Virginia Hospital over a period of 12 years, and to discuss its significance. The results are recorded with a pride of accomplishment in surgery which is not exclusively local. As the result of contributions to medical knowledge throughout the world, the same progress could be demonstrated in every progressive surgical clinic.

The decrease in surgical mortality to be demonstrated is, of course, the result of revolutionary improvements in surgical practice during the last generation, improvements that have had a steady acceleration so that the last five years have seen the greatest gain of all. The 12 years under scrutiny

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

here represent the accretion of advances of many preceding years. These developments in surgery have been largely directed toward the more complete protection of the surgical patient as a whole from the effects of both disease and operation.

We need not discuss in detail any of the factors which make up the total pattern. There are at least six major elements to be mentioned, not necessarily in the order of their relative importance: (1) An increase in the accuracy of the diagnosis of disease and particularly of the diagnosis of surgical complications, such as thrombophlebitis and shock. (2) A stricter attention to and a more accurate management of water, electrolyte, protein and vitamin balances in the surgical patient. (3) A better understanding of the rôle of blood volume and its control. (4) Major developments in the field of anesthesia and in the mechanical control of respiratory complications. (5) The introduction of specific chemotherapeutic and antibiotic substances. (6) The adoption of certain special therapeutic measures in common surgical diseases, such as those developed for the treatment of phlebothrombosis, thrombophlebitis, jaundice, thyrotoxicosis, intestinal obstruction, and others. The first five of these affect the chance of recovery of any patient with major surgical disease. The sixth has its influence on general surgical mortality by protecting the individual patient suffering from a specific condition.

MATERIAL

We report the over-all mortality in 20,137 cases cared for by the Department of Surgery and Gynecology of the University of Virginia over a period of 12 years (1934 to 1945, inclusive). These cases include all direct admissions to the surgical service, whether or not operation was performed.* As in any surgical service, operative cases represent an overwhelming majority of the total number. The operations were performed in more than half of the total number of cases by resident surgeons, men in the fifth or sixth year of graduate training or, in the less exacting material, by assistant residents under the supervision of the resident. In all ward cases the decisions were made by a visiting surgeon, and in practically all major operative cases from the wards the exposed pathologic changes were observed by a visiting surgeon and the choice of surgical management determined by him in consultation with the operator. Under this supervision the resident staff performed almost all the major surgical operations on ward patients. Preoperative preparation, postoperative care and the treatment of nonoperative cases were closely followed by visiting surgeons in daily rounds.

During the period reported no striking changes occurred in the type of material admitted to the surgical service with the exception of a marked increase in major thoracic surgery. During this period also, as will be noted later, the threshold of operability was progressively lowered.

* Transfers to the surgical service are not included. The mortality figures, therefore, have relative rather than absolute values.

MORTALITY OF SURGICAL DISEASE

The yearly number of deaths has been calculated as a percentage of each year's cases, constituting the surgical mortality for that year. The mortality percentages have been separately calculated also for each six-year period.

A comparison of the over-all mortality with that of a single illustrative condition appeared useful. For this comparison mechanical intestinal obstruction was chosen, in the first place because it has a relatively large mortality rate in which any change could be more confidently interpreted and in the second place because the data were readily available from a general study of the subject under preparation by one of the authors. The mechanical intestinal obstruction material consists of all cases so diagnosed during the period, whether or not operation was performed.* In order to obtain significantly large figures, the mortalities were calculated on each half of the total material rather than yearly. For the first six-year period there were 147 cases of intestinal obstruction and for the second, 186 cases..

RESULTS

The curve of annual percentages of surgical deaths (Chart 1) shows an almost continuous drop from the beginning of the period to the close, descending from a high of 7.1 per cent in 1934 to a low of 2.5 per cent in 1945. This represents a decline of almost two-thirds in the absolute values. If one compares the first six years with the remaining six years, the average figures are 6.3 per cent for the former as compared to 3.4 per cent for the latter (Table I), a decline of 46.1 per cent (Chart 2).

During the first six years the mortality from intestinal obstruction was 27.2 per cent, and during the last six years, 15.0 per cent (Table I). This represents a decline in mortality of 44.9 per cent (Chart 2), which is almost exactly the corresponding decline in mortality for all cases admitted to the surgical service.

DISCUSSION.—The literature abounds with reports of steadily improving mortality rates in specific surgical diseases, both with and without operation. We have been able to find no report presenting even a rough over-all picture such as we have presented except for data scattered in relatively inaccessible annual reports of hospitals. Without the more detailed analysis to which the figures might be susceptible, there can be derived from them at least four implications that should be a part of current surgical thought.

An obvious result of declining surgical mortality has been the expanding surgical horizon, particularly the invasion of new fields and the lowering of the threshold of operability. It is now justifiable to undertake surgical operations of an extent that a generation ago no surgeon would have even considered. It must be noted again that the period studied coincides with a period of great increase both in number and extent of intrathoracic proce-

* A few cases of relatively rare occurrence presenting special problems were excluded from the data reported. These were instances of congenital atresia, Hirschsprung's disease, fecal impaction, benign rectal stricture and malfunctioning colostomy.

dures. It also coincides with a general surgical trend towards a more radical approach to cancer and particularly to intra-abdominal cancer. One need only cite the extensive resections for cancer reported by Brunschwig,¹ Lahey,² and others, as well as expansion in limits of operability, such as that presented by David and Gilchrist³ for cancer of the rectum. These are only examples to illustrate the point. A similar trend has been obvious in the surgical approach to cancer at the University of Virginia Hospital. We are not immediately concerned with the justification for multiple visceral resection for abdominal

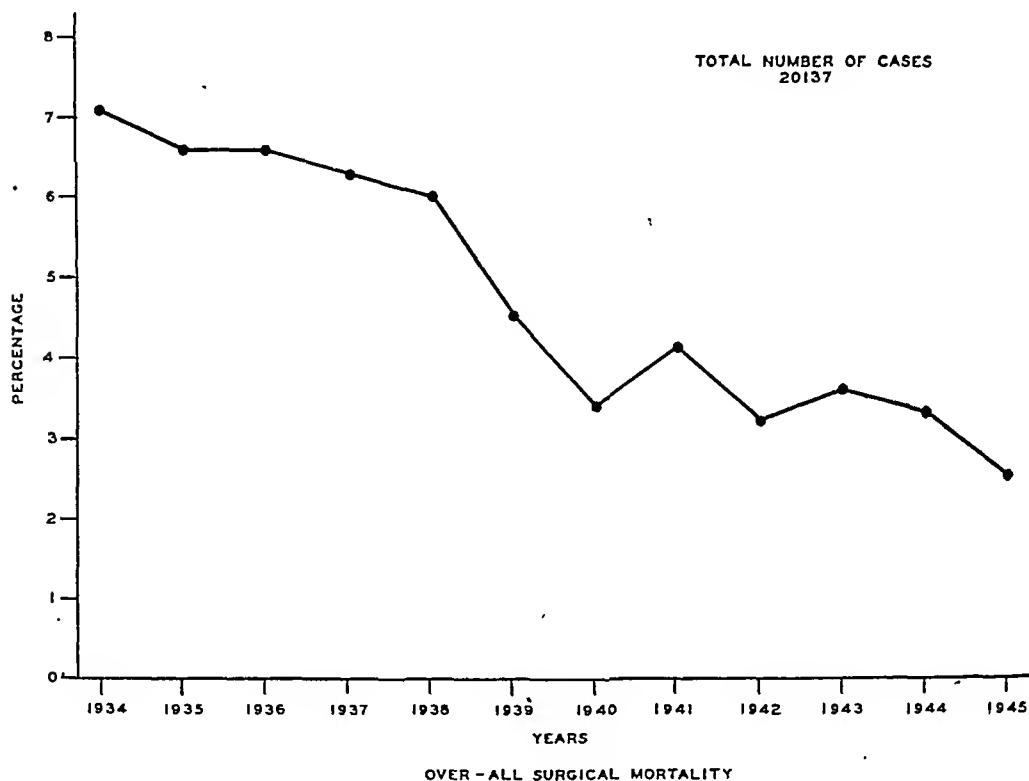


CHART I.—Annual hospital mortality, Department of Surgery and Gynecology, University of Virginia Hospital, 1934 through 1945, including all cases (20,137) treated with and without operation.

cancer, but solely with its relationship to total hospital mortality. In spite of the fact that these developments in surgery have been taking place, developments theoretically to be expected to increase mortality, that phenomenon has not occurred. The decline in surgical mortality would unquestionably have been even more dramatic if these bold ventures had not been undertaken.

In the measurement of improvements in the surgical mortality of specific diseases and particularly of specific diseases studied in relation to new therapeutic devices, the curve of total surgical mortality has a continuing significance. Brooks⁴ compared the mortality of surgical operation in the aged

with the life-expectancy of the general population in the same age-group. Balfour⁵ presented before this society the late results of surgery in cancer of the stomach against the background of a similar life-expectancy curve. Other studies of a like nature have been made, all of which illuminate the significance of surgical results. Many reported instances of improvement in surgical mortality have been ascribed to the adoption of individual therapeutic procedures without measured consideration of the results to be expected without such procedures. An hypothetic example may be given. In our own treatment of intestinal obstruction a drop of almost 50 per cent occurred in the mortality when two six-year periods were compared. During the later period, following the report of Fine, Hurwitz and Mark,⁶ plasma adminis-

TABLE I

ACTUAL MORTALITY OF ALL CASES AND OF CASES OF INTESTINAL OBSTRUCTION IN THE YEARS 1934-1939, INCLUSIVE, AS COMPARED TO THE YEARS 1940-1945, INCLUSIVE. THESE FIGURES REPRESENT BOTH OPERATIVE AND NONOPERATIVE CASES.

Years	All Cases		Intestinal Obstruction	
	Number	Mortality	Number	Mortality
1934-1939.....	8,251	6.3%	147	27.2%
1940-1945.....	11,886	3.4%	186	15.0%

tration was introduced as an adjuvant to other therapy in small bowel obstruction. It would be easy to ascribe to this measure a major influence in the improvement in results were it not that the mortality of other surgical disease dropped correspondingly. In the light of that comparison any effect of plasma administration cannot be descried. In other words, statistical appraisal of surgical procedures should not be attempted without either employing the alternate case method in a large series, or with a full knowledge of the total decline in surgical mortality in the individual institution during the period studied.

Harvey Cushing, at the time he took over the professorship at Harvard and the surgical direction of the Peter Bent Brigham Hospital, wrote in a letter to his colleague, Dr. Christian, as follows⁷: "I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work." This rhetorical exaggeration from a man whose hands were swift instruments of extraordinary accuracy and delicacy expresses a truth of which a hint is seen in the present data. The material presented, as already stated, consists in more than half the cases of operations of all magnitudes carried out by relatively inexperienced technicians, the residents, under the supervision of experienced surgeons. Since the decline in surgical mortality here reported has occurred in spite of the participation of a large number of inexperienced technicians, it can be considered due less to increasing technical skill than to the develop-

ment of measures for the protection of the surgical patient applied under the advice and direction of experienced surgeons. A progressive drop in mortality in a series of cases operated upon by an individual surgeon can be ascribed in part to increasing technical skill, but his increasing knowledge of disease and his adoption of improvements in general surgical care may play the major rôle. We would not deny that technical dexterity has a place in

surgical results, but we would present for consideration, as have Cushing, and others,⁸ the idea that it may be less important than other factors.

Finally, the urgency of repeatedly presenting surgical results to the profession at large must be considered. The success of surgery as a whole and the opportunities for surgery to accomplish the most good for the greatest number of sick people depends in considerable part upon its reputation among family doctors and consultants in internal medicine. Many of these practitioners base their judgment of surgical mortality on what they were taught during their surgical courses in medical school. They do not have ready access to surgical journals in which recent statistical data are usually published. It is the task of these men to give the primary advice leading to surgical consultation. Theirs is the first choice; and

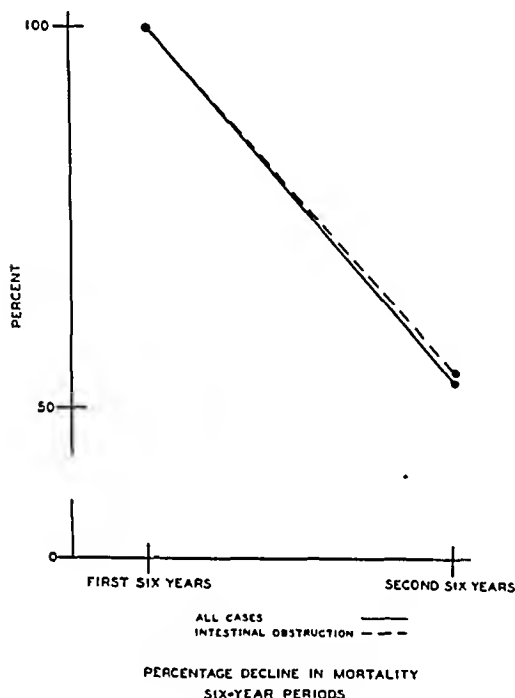


CHART 2.—Comparative percentage decline in mortality rate of all cases and of cases of intestinal obstruction in two six-year periods, 1934-1939 and 1940-1945, respectively.

it is quite natural that they will base that choice on their knowledge, no matter where or when derived, of surgical risk. Many conscientious practitioners, of course, familiarize themselves with modern surgical risk and give advice based on sound information, but many do not. There appears, therefore, to be some need for surgery to broadcast its accomplishments beyond its own sphere, not with boastful intent but for the purpose of bringing surgical relief to more people. If it were possible to present periodically between the covers of a single publication the surgical mortalities attained by a group of representative hospitals, the internist and the family doctor would have a ready source of reference for this information. Such a compilation would also furnish all surgeons, including those working under less favorable circumstances, a yardstick for their own accomplishments. We suggest that one of the surgical societies study methods of accomplishing this needed end.

MORTALITY OF SURGICAL DISEASE

REFERENCES

- ¹ Brunschwig, A.: Extending Surgery in Treatment of Cancer of Colon. *Surgical Clinics of North America*, 24, 185-202, 1944.
- ² Lahey, F. H.: Total Gastrectomy, Splenectomy, Resection of Left Lobe of Liver, Omentumectomy, and Colectomy upon One Patient in One Operation. *ANNALS OF SURGERY*, 119, 222-224, 1944.
- ³ David, V. C., and Gilchrist, R. K.: Extension of Border Line of Operability in Cancer of Rectum. *ANNALS OF SURGERY*, 115, 566-573, 1942.
- ⁴ Brooks, B.: Surgery in Elderly Patients. *ANNALS OF SURGERY*, 105, 481-495, 1937.
- ⁵ Balfour, D. C.: Factors of Significance in the Prognosis of Cancer of the Stomach. *ANNALS OF SURGERY*, 105, 733-740, 1937.
- ⁶ Fine, J., Hurwitz, A., and Mark, J.: A Clinical Study of the Plasma Volume in Acute Intestinal Obstruction. *ANNALS OF SURGERY*, 112, 546-556, 1940.
- ⁷ Fulton, J. F.: Harvey Cushing, A Biography. Page 352, Springfield, Illinois, 1946.
- ⁸ Cole, W. H.: Symposium on Abdominal Surgery—Introduction. *Surgical Clinics of North America*, 24, 1-2, 1944.

University of Virginia Hospital
Charlottesville, Va.

DISCUSSION.—DR. JOHN C. BURCH, Nashville, Tenn.: This is a timely subject. Doctor Lehman's data clearly reflect the great progress made in reducing surgical mortality. In my opinion this decrease is general in the better clinics. Many of us are slow to accept change; for them, this paper will prove a needed stimulus. For our medical colleagues who harbor exaggerated ideas concerning the risks of surgery, it should prove enlightening. They may even refer a few more patients in an earlier stage of their disease. For the medical educator, the inference is plain. Many of the things taught ten years ago are not the things emphasized today. Much new progress must be assimilated by the profession. It is clear that surgery is a field of continuing study. Unless this primary fact is emphasized as the foundation of all surgical training, our young surgeon will find himself in the ranks of those unwilling to accept change. From an experience with many recent graduates it is my opinion that much remains to be accomplished along these lines.

Doctor Lehman did not stress the equally great strides which have been made in decreasing morbidity and shortening convalescence. Great improvement in the handling of surgical cases has resulted from a better understanding of the physiology of bed rest. The results of early rising are truly phenomenal. In recently reviewing a series of about 1,400 hysterectomies performed over a period of years, a striking reduction in the number of cases of thrombophlebitis was noted. It is, of course, difficult to attribute this to any one cause, but early mobilization of the surgical patient has undoubtedly played a most important rôle.

PRIMARY PULMONARY MALIGNANCY TREATED BY RESECTION*

AN ANALYSIS OF 129 CASES

ALTON OCHSNER, M.D., MICHAEL E. DeBAKEY, M.D.,
AND
LEONARD DIXON, M.D.
NEW ORLEANS, LA.

FROM THE DEPARTMENT OF SURGERY, SCHOOL OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA,
AND THE DIVISION OF SURGERY, OCHSNER CLINIC, NEW ORLEANS, LA.

DURING THE ALMOST 11-YEAR PERIOD beginning January 1, 1936, and ending December 1, 1946, there were observed in our private practice and on our service in Charity Hospital of Louisiana, at New Orleans, 360 patients with pulmonary malignancy, 129 of whom were submitted to pulmonary resection. Two hundred and sixty-one cases, in 113 of which resection was performed, occurred in private practice and 99, in 16 of which resection was done, at Charity Hospital. It is the purpose of this report to present an analysis of the 129 resected cases, including the follow-up observations made on all patients who survived surgery.

INCIDENCE

Recent literature on carcinoma of the lung has emphasized the apparently increasing incidence, and in previous publications we have considered this phase of the subject.^{15, 18, 19} On the basis of both reports in the literature and our own experience the statement is justified that carcinoma of the lung has become one of the most frequently encountered malignant neoplasms, and that the lung is now preceded only by the stomach as a primary site of cancer.

Comparative statistics from Charity Hospital of Louisiana, at New Orleans, bear out these conclusions. During the ten-year period ending January 1, 1946 (Chart 1) the yearly incidence of carcinoma of the stomach, while it showed transient increases and decreases, was substantially unchanged, whereas the incidence of carcinoma of the lung showed a general slight increase. The rate for Negroes was practically level during this period, although carcinoma of the stomach was considerably more frequent in this race, while the incidence of pulmonary malignancy among white patients showed a definite general increase. The data suggest that the racial distribution of the disease may be significant. During the period in question the ratio of colored to white admissions was about equal, but the incidence of carcinoma of the lung was approximately 2 to 1 in favor of the white race (Chart 2).

Only seven (5.4 per cent) of the 129 resections were done in Negro patients, but the small number is not significant. The white preponderance is

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

Incidence of Carcinoma of Lung and Stomach
Based upon Admissions at Charity Hospital

Jan.1, 1936 to Jan.1, 1946

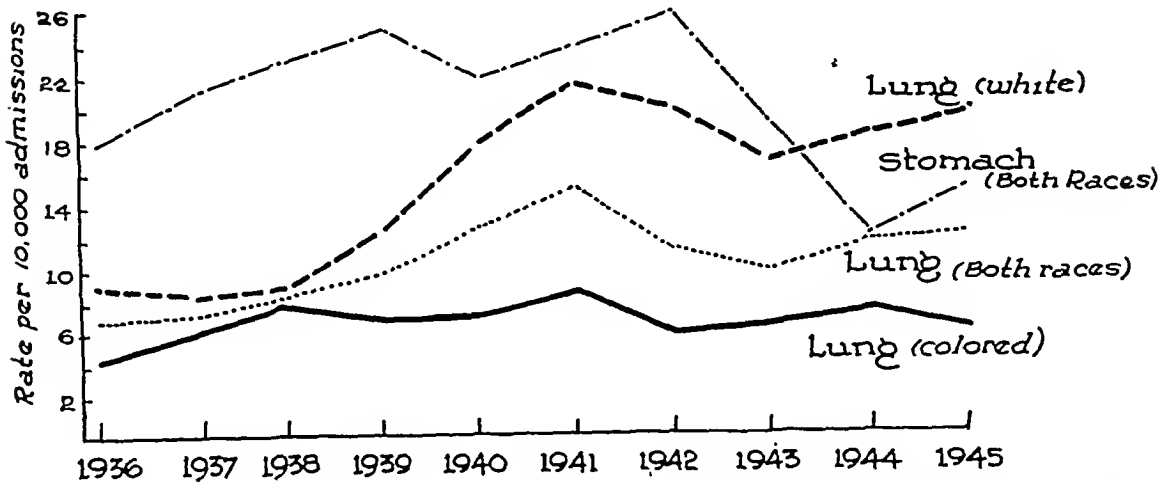


CHART 1.—Comparative incidence of carcinoma of the lung and stomach in the white and colored races based upon admissions at the Charity Hospital in New Orleans during the ten-year period, 1936–1945, inclusive.

Race Incidence of Carcinoma of Lung and Stomach
Based on Admissions at Charity Hospital

Jan.1.1936 to Jan1,1946

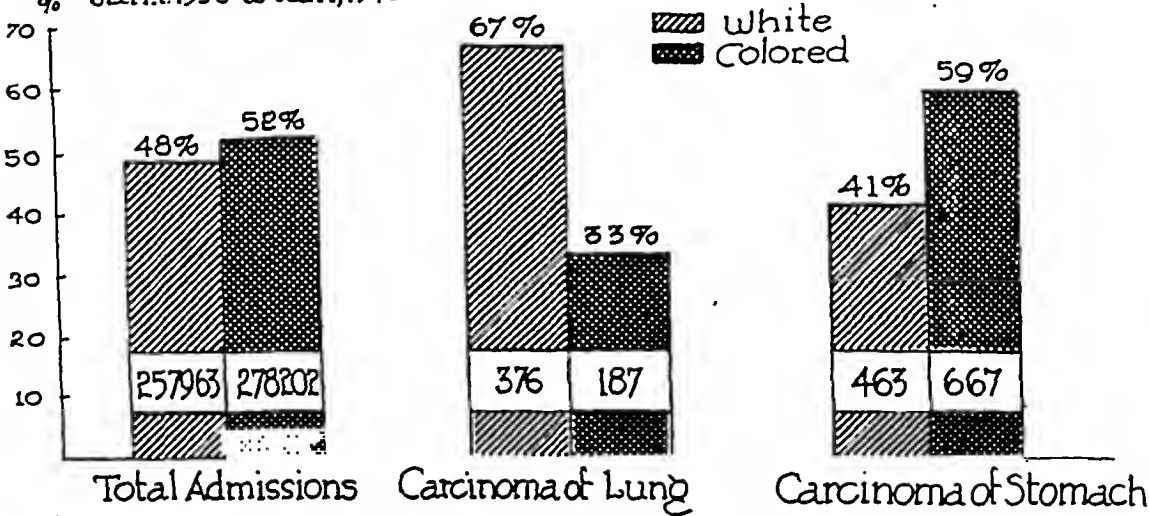


CHART 2.—Graphic representation of incidence of carcinoma of the lung and stomach in the white and colored races compared with total admissions of the two races in the Charity Hospital, New Orleans, Louisiana, during the ten-year period, 1936 to 1945, inclusive.

readily explained by the large proportion of cases treated at hospitals which serve only white patients.

Sex.—All experience indicates that carcinoma of the lung is predominantly a disease of males, though no satisfactory explanation for the sex discrepancy has been advanced. In the 360 clinical cases observed by us there

Pulmonary Malignancy treated by Resection
129 cases

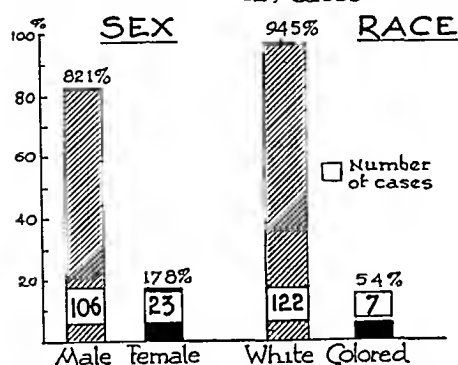


CHART 3.—Graphic representation of the sex and race incidence in the authors' series of 129 cases of pulmonary malignancy treated by resection.

were 311 males (86.3 per cent) and 40 females. Among the 129 resected cases there were 106 males (82.1 per cent) and 23 females (Chart 3). These figures are in line with the proportions found in 8,575 collected cases of carcinoma of the lung, in which 6,769 patients (78.9 per cent) were males and 1,806 females.¹⁵ If so-called mixed tumors (adenomas) are considered, the sex ratio is distinctly different, there being a small female preponderance in this type of growth.

Pulmonary Malignancy—Age Incidence

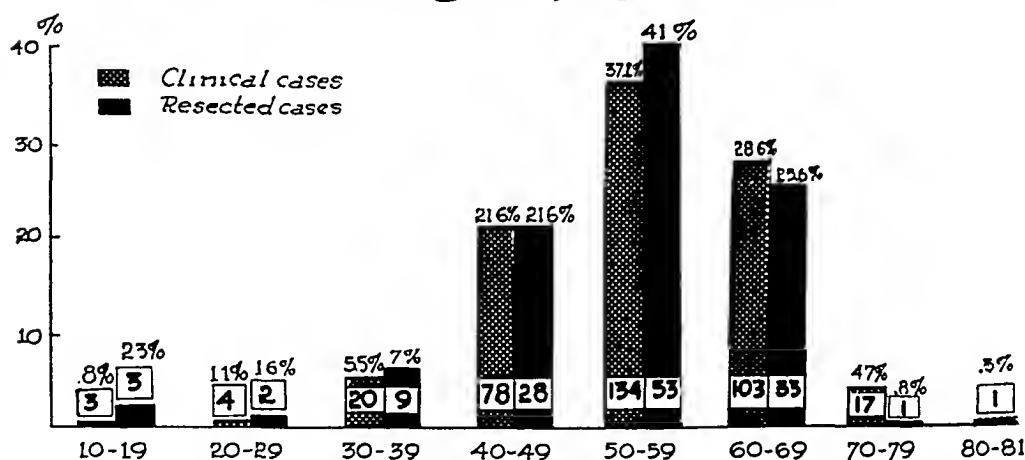


CHART 4.—Graphic representation of age-incidence by decades in the authors' series of 360 clinical and 129 resected cases of pulmonary malignancy.

Age.—It is the general experience that while carcinoma of the lung may occur at almost any period of life, it is most frequent in the 5th, 6th, and 7th decades. In our total series, as well as in our resected cases, almost 90 per cent of the patients were in this age-group (Chart 4).

ETIOLOGY

The numerous explanations advanced to account for the apparent increase in incidence in carcinoma of the lung have been reviewed in previous publications and will not be discussed here.^{15, 18, 19} In the 129 resected cases no factor was found which might bear a significant relationship to the occurrence of the disease. Neither occupation nor smoking habits, which some reports, including our own, have stressed as of possible etiologic significance, seemed of any special significance in this particular series (Charts 5 and 6).

Pulmonary Malignancy treated by Resection
129 cases

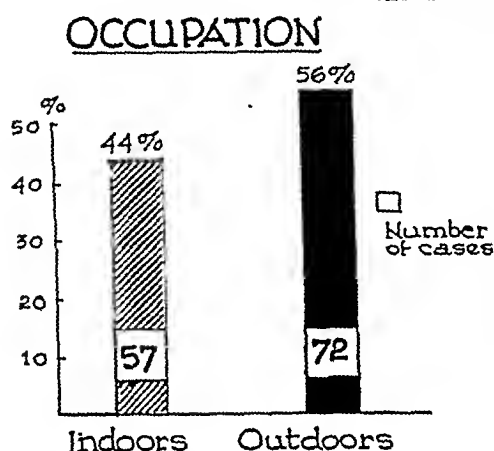


CHART 5.—Graphic representation of type of occupation in the authors' series of 129 cases of pulmonary malignancy treated by resection.

Pulmonary Malignancy Treated by Resection
129 cases

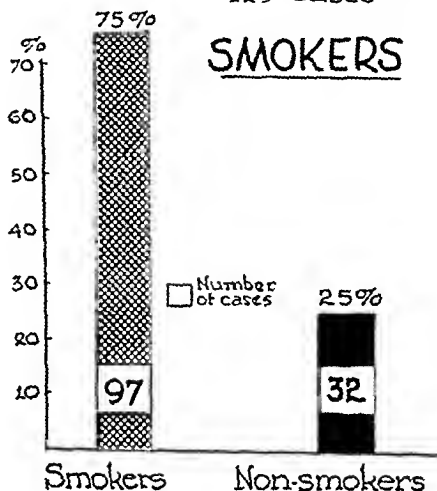


CHART 6.—Graphic representation of incidence of smokers and nonsmokers in the authors' series of 129 cases of pulmonary malignancy treated by resection.

PATHOLOGY

The pathologic picture in our series of cases of carcinoma of the lung will form the subject of another report, and will not be discussed at this time. It is important to note, however, that the 129 resected cases included 124 cases of bronchiogenic carcinoma, two cases of fibrosarcoma, and one case each of melanomasarcoma, neurogenic sarcoma, and lymphoblastoma. In 76 cases the involvement was on the right side, and in 53 on the left (Chart 7), which is in correspondence with most of the reports in the literature. The greater frequency of occurrence on the right side possibly can be explained on the basis of the larger size of the right lung. The incidence of involvement in the upper lobe on each side and in the right lower lobe was practically the same (Chart 7).

CLINICAL PICTURE AND DIAGNOSTIC CONSIDERATIONS

The clinical picture of carcinoma of the lung is not sharply characteristic, and this fact, plus the usually insidious onset, undoubtedly explains the fre-

quent delay in diagnosis. An analysis of the 129 resected cases, which form the basis of this study, bears out other reports, and indicates that the most common symptoms are cough, loss of weight, discomfort or pain in the chest, and hemoptysis, in about that order of frequency (Chart 8). The next most frequent clinical manifestations, in addition to a history of previous respiratory infection, are dyspnea, wheezing, and changes in the voice (Chart 8).

This series also makes clear how important it is to remember that in many cases, and particularly in the earlier cases, not more than one or two complaints may be present. The paucity of symptoms accounts for the difficulty frequently encountered in framing a characteristic clinical picture in the early stages of the disease and makes it doubly important to bear constantly in mind the possibility of pulmonary malignancy in any patient over 40 years of age,

Pulmonary Malignancy Treated by Resection
SITES OF INVOLVEMENT

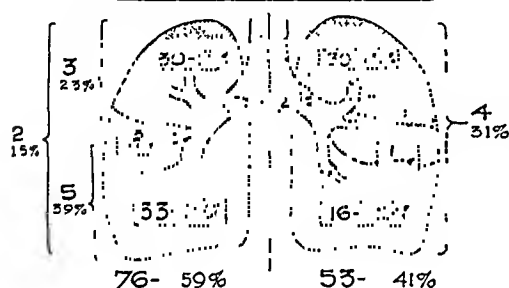


CHART 7.—Diagrammatic representation of incidence of sites of involvement in the authors' series of 129 cases of pulmonary malignancy treated by resection.

Pulmonary Malignancy treated by Resection
COMPARATIVE INCIDENCE OF RECORDED SYMPTOMS

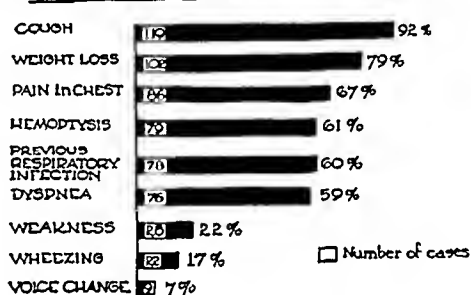


CHART 8.—Graphic representation of the incidence of recorded symptoms in the authors' series of 129 cases of pulmonary malignancy treated by resection.

particularly any male patient, with symptoms referable to the respiratory system. The recollection of the possibility is the key to improvement in the diagnosis of early cases.

The physical findings in carcinoma of the lung vary considerably and depend upon the site, size, and direction of growth of the tumor. Significant findings are more likely to be encountered if the tumor encroaches upon the lumen of the larger bronchi or upon the pleura. Generally speaking, the physical findings, like the symptoms, are not characteristic, and in early cases the examination is likely to be negative.

Roentgenology.—Of all diagnostic methods in carcinoma of the lung the most important is roentgenologic examination. It resulted in a positive diagnosis in 105 of our 129 resected cases, 81 per cent (Chart 9), which is in accordance with the 60 to 80 per cent of successful diagnoses reported by this method in the literature. The most frequent error, the diagnosis of lung abscess, was actually not usually an error, since in almost every case thus

diagnosed an abscess was actually present in association with the pulmonary malignancy.

Bronchography (with lipiodol) is a very useful diagnostic procedure in certain types of cases, particularly those in which the tumor is not of sufficient size or density to cast a shadow on plain roentgenologic examination and in which the lesion is one of the small bronchi and, therefore, cannot be visualized by bronchoscopy.

It cannot be too strongly emphasized that carcinoma of the lung will continue to be overlooked until all physicians develop the habit of routine roentgenologic examination of all patients with any symptoms referable to the chest unless they are clearly due to some other cause. The practice should be routine even when physical findings are negative. In four cases in this series the growth was discovered because roentgenologic examination was part of the diagnostic routine. Despite the accidental discovery, and the fact that all growths could be resected, histologic study of the hilar nodes showed that metastasis had already occurred in three of the four patients.

Bronchoscopy and Biopsy.—The most reliable method of diagnosis in bronchogenic carcinoma is visualization of the tumor by bronchoscopy and examination of a biopsied specimen. According to the literature, which is borne out by our own experience, the method is accurate in from 60 to 80 per cent of all cases, the proportion of correct diagnoses varying with the location of the tumor. Fortunately, the majority of malignant tumors of the lung are in bronchial segments which can readily be visualized. Lesions in the upper lobe and in the peripheral portion of the lung are much less likely to be diagnosed by bronchoscopy, and sometimes cannot be diagnosed at all by this method.

Bronchoscopy was performed in 112 (87 per cent) of our 129 resected cases (Chart 10), in 68 of which (61 per cent) a biopsy specimen could be obtained. The specimen was positive in 55 (81 per cent) of the 68 cases.

X-RAY DIAGNOSIS

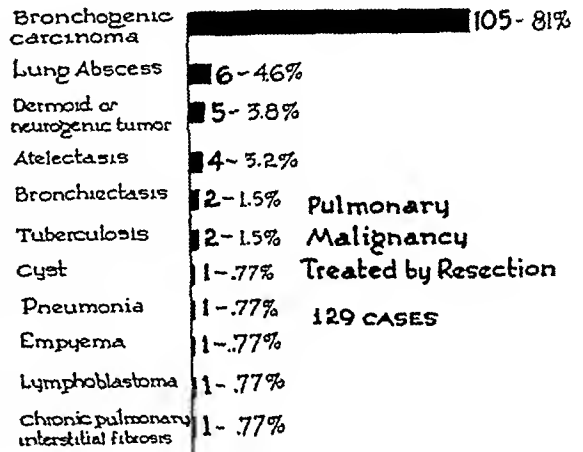


CHART 9.—Graphic representation of roentgenologic diagnoses made in the authors' series of 129 cases of pulmonary malignancy treated by resection.

Pulmonary Malignancy treated by Resection 129 CASES RESULTS OF 112 BRONCHOSCOPIC EXAMINATIONS

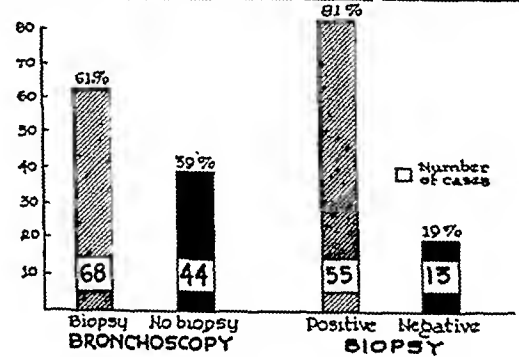


CHART 10.—Graphic representation of results of 112 bronchoscopic examinations performed in the authors' series of 129 cases of pulmonary malignancy.

Bronchoscopy was deliberately omitted in 17 of the 129 cases because roentgenoscopic examination revealed the growth to be so peripherally located that visualization by this means was obviously impossible.

Other Diagnostic Methods.—The microscopic examination of expectorated material or of material aspirated at bronchoscopy to determine the presence or absence of tumor cells is a diagnostic method of increasing importance which should be employed much more frequently than it is. It requires considerable experience, but in the hands of experienced observers it is of great value, particularly in cases in which bronchoscopic visualization of the tumor is not possible.

TABLE I

INCIDENCE OF OPERABILITY AND RESECTABILITY IN PRIMARY PULMONARY MALIGNANCY

Authors	Number of Cases Observed	Cases Explored		Cases Resected	
		No.	Per Cent	No.	Per Cent
Edwards.....1938	172	28	16.3	13	7.6
Churchill.....1940	156	52	33.3	27	17.3
Burnett.....1941	102	34	33.3	12	11.7
Fetter.....1943	31	6	19.3	0	0
Overholt.....1943	165	80	48.5	41	24.8
Brock.....1943-44	330	45	13.6	22	6.6
Clagett and Brindley.....1944	493	90	18.2	45	9.1
Rienhoff.....1944	...	181	39
Adams.....1946	157	94	59.8	49	31.2
Carnes, Cesanelli, and Tricerri. 1946	107	21	19.6	12	11.2
Graham.....1946	221	112	50.7	39	17.6
Lindskog.....1946	100	32	32	12	12
Total.....	2,034	594*	29.2	272	13.4
Authors.....	360	210	58.3	129	35.8

* Actually this figure is probably somewhat higher, since it does not include a small proportion of cases in which operation was refused.

Aspiration biopsy is mentioned only to be condemned. The danger of implanting metastases in the pleura and chest wall is not merely theoretical. The implantation occurred in two of our own cases and has been reported by others.^{8, 17, 18} In our opinion the method is justifiable only in cases of suspected pulmonary malignancy which are obviously inoperable and in which an accurate diagnosis is of great importance.

If other methods fail, and if the diagnosis of carcinoma of the lung cannot positively be excluded, exploration of the chest should be regarded as part of the diagnostic procedure. When properly performed it is attended with a minimum mortality, and it frequently reveals an early, and, therefore, operable, growth. In our series of 210 cases in which exploration was done a positive diagnosis was established prior to operation in 146 (69.5 per cent).

OPERABILITY

The only satisfactory treatment of carcinoma of the lung is surgical extirpation of the involved area, preferably by pneumonectomy. Upon that point

there is general agreement. Unfortunately, there is also general agreement that the incidence of operability is discouragingly low. Thus, it may be observed from Table I that in 2,034 cases of primary pulmonary malignancy collected from the literature, operation appeared feasible and exploration was done in 594 (29.2 per cent), but that resection actually was possible in only 272, or 13.4 per cent. While there are understandably considerable variations in the incidences of operability and resectability among these reported series, there is an encouraging trend toward higher incidences among the more recent reports. Our own experience (Charts 11 and 12) is in accord with these latter reports.

In the 360 cases of pulmonary malignancy diagnosed clinically, 109, or 30 per cent, were clearly inoperable. Of the 251 cases regarded as operable, surgery was refused by the patients in 41, or 10 per cent. Of the 210 cases explored, 81 proved inoperable, or 38.5 per cent, leaving 129 cases, or 35.8 per cent, of the whole group, in which resection could be done. What this amounts to is that of every three cases of clinical pulmonary malignancy only one eventually proves resectable. When it is recollected how many patients die after resection or, if they survive, die after discharge from the hospital, these figures are even worse than they seem.

Technical details have been discussed at length in previous communications,^{13, 14, 16, 18} and no attempt will be made to review them here. Pneumonectomy, as already mentioned, we consider the procedure of choice. It was performed in 127 of the 129 cases. Simple lobectomy was done in the other two cases, in one because at the time of operation the condition was thought to be inflammatory and in the other as a palliative procedure, to relieve the patient of severe and discomforting manifestations of an accompanying lung abscess.

Although both the anterior and the posterolateral approaches were employed, the anterior approach is preferred when it is not contraindicated. The posterolateral approach is chiefly used in cases in which it is believed that dense adhesions may be encountered, posteriorly and laterally.

In an effort to increase the limits of operability in the cases explored, certain supplementary procedures were carried out in some patients in whom the tumor had extended beyond the confines of the lung. For this reason ligation of the large hilar vessels was done within the pericardial cavity in 18 cases, resection and suture of a portion of the auricle in eight cases, resection of part of the diaphragm in seven cases, and resection of a portion of the chest wall in six cases (Chart 13).

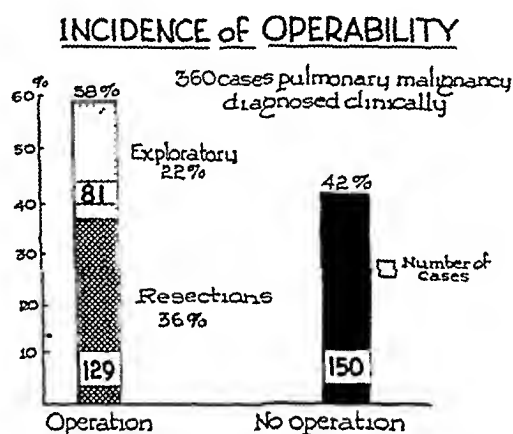


CHART 11.—Graphic representation of the incidence of operability in the authors' series of 360 cases of pulmonary malignancy.

POSTOPERATIVE MORBIDITY AND MORTALITY

Postoperative infection, in the form of empyema, occurred in 15 of the 129 cases, or 11.6 per cent. In five instances, or 3.8 per cent, the infection was the result of a blown bronchus (Chart 14). Only one of the five patients in this

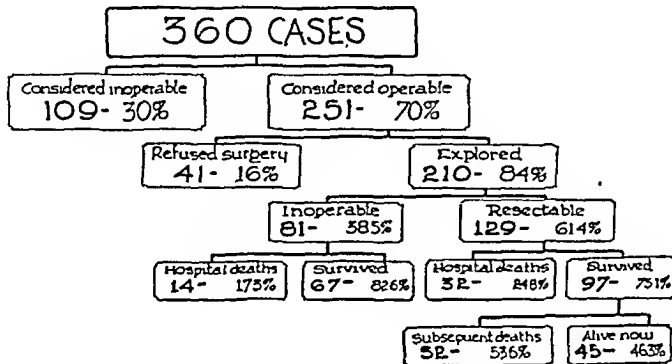
Results in 360 Cases of Pulmonary Malignancy
Diagnosed Clinically

CHART 12.—Schematic representation of the results in the authors' series of 360 clinical cases of pulmonary malignancy.

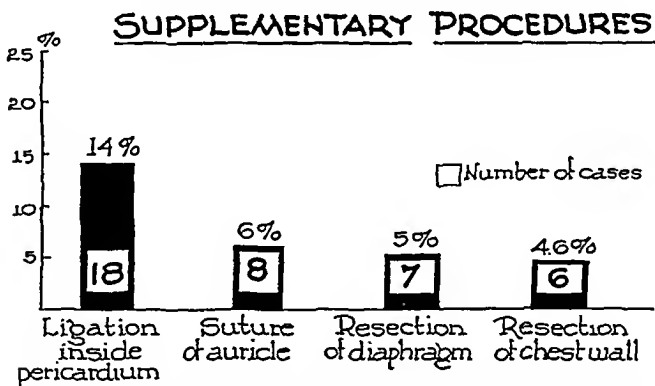
Pulmonary Malignancy Treated by Resection
129 CASES

CHART 13.—Graphic representation of supplementary procedures performed in the authors' series of 129 cases of pulmonary malignancy treated by resection.

group survived. Our experience with chemotherapy, whether in the form of sulfonamide drugs or penicillin, has not been very encouraging, and it is our general impression that the introduction of these agents has not materially influenced the incidence of the morbidity of this complication.

PULMONARY MALIGNANCY

Of the 129 patients in whom resection was done, 32, or 24.8 per cent, died in hospital (Chart 15). Cardiovascular complications (Chart 16) were responsible for 15 deaths, almost half of the total number, and respiratory infections, especially pneumonia, for the next largest number. In the remaining eight deaths the cause of the fatality was hemorrhage in four, and these

Pulmonary Malignancy Treated by Resection
129 CASES

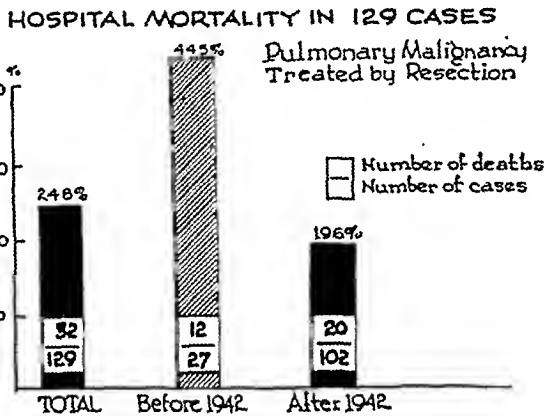
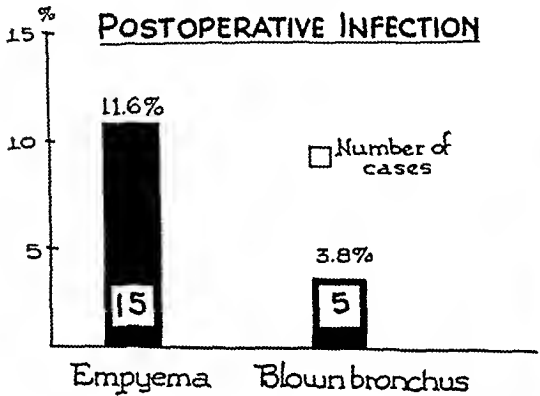


CHART 14.—Graphic representation of incidence of postoperative infection in the authors' series of 129 cases of pulmonary malignancy treated by resection.

CHART 15.—Graphic representation of hospital mortality in authors' series of 129 cases of pulmonary malignancy treated by resection.

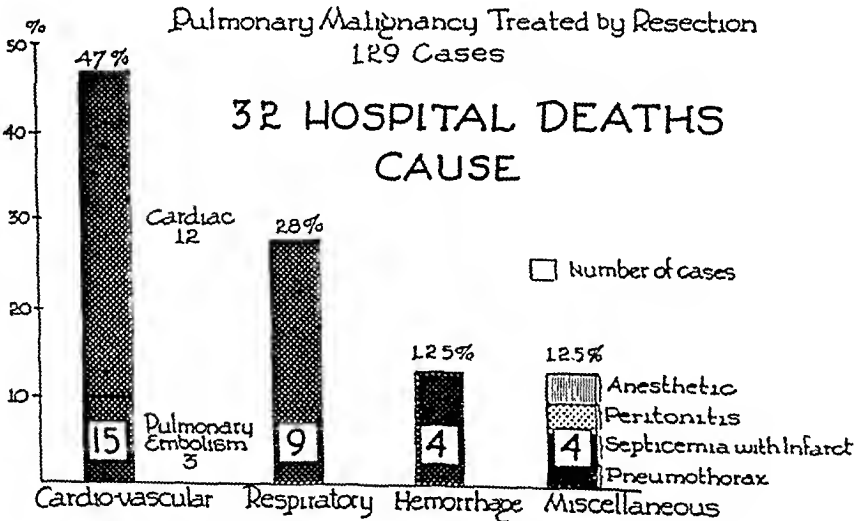


CHART 16.—Graphic representation of cause of hospital deaths in authors' series of 32 cases of pulmonary malignancy.

fatalities, as well as those due to anesthetic causes and to pneumothorax, may be classified as due to technical errors and, therefore, preventable. The relatively high incidence of cardiovascular complications, however, is for the most part not preventable. They represent a risk which must be assumed in pneumonectomy for carcinoma of the lung unless the criteria of operability are

so strictly limited that patients in whom they are likely to occur are excluded from surgery and are, thus, denied their only chance of salvage.

The largest number of hospital deaths, 12, or 37.5 per cent, occurred within 24 hours of operation (Chart 17). Seven others occurred before the 5th day, or 22 per cent, seven before the 10th day, or 22 per cent, four before the 15th day, or 12.5 per cent, and one each on the 18th and 43rd day, respectively.

The major portion of the immediate post-operative mortality, thus, occurred within the first ten days, and approximately half of the deaths in this group occurred within the first 24 hours after operation, usually from cardiovascular causes (Chart 17).

When the resected cases are divided into those which were operated upon before January 1, 1942, and those which were operated upon after that date, it is apparent that the hospital mortality in the former group is 44.5 per cent and in the latter group 19.6 per cent (Chart 15). It is fair to assume that the reduction is attributable to improvement in technic, as well as preoperative and postoperative care. Among the patients who survived operation, the postoperative hospital stay days prior to 1942 averaged 32.3, and after that date 13.1. The shortened period of hospitalization in the second period is also a reflection of the improvements mentioned (Chart 18).

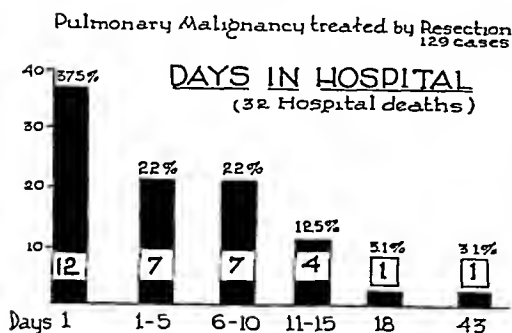


CHART 17.—Graphic representation of postoperative survival period of 32 hospital deaths in authors' series of pulmonary malignancy treated by resection.

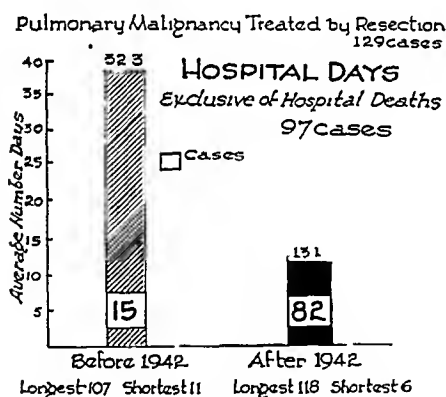


CHART 18.—Graphic representation of period of hospitalization (exclusive of hospital deaths) in the authors' series of pulmonary malignancy treated by resection, according to whether operation was performed before or after 1942.

of us. At this time, our report concerns only the absolute survival rates, without reference to the presence or absence of recurrence at the last examination or to any other factor which might conceivably influence the patient's chances for survival.

It seems scarcely necessary to point out that because the 107 patients involved in these calculations were operated upon at varying periods of time over the past ten years, the number of cases in each time-category is different, and that the numbers become smaller as the possible survival-time increases.

FOLLOW-UP OBSERVATIONS

Every patient in this series who was submitted to operation six months, or more, ago and who left the hospital alive has been followed up to date, the examination in the great majority of cases being made personally by one

PULMONARY MALIGNANCY

Patients operated upon only a year ago, for instance, obviously have had no opportunity to survive longer than a year. Incidentally, it would be very desirable if surgeons who have series of lobectomies to report should calculate

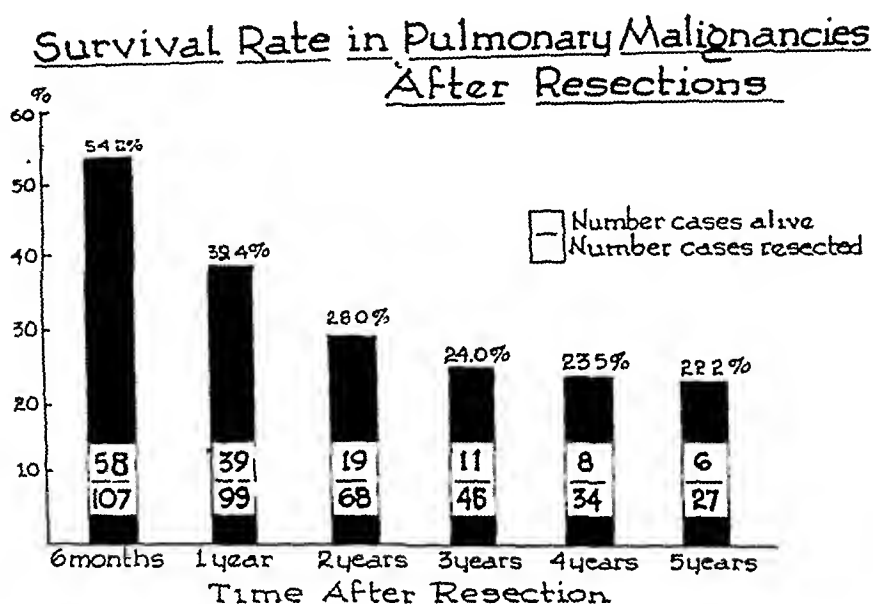


CHART 19.—Graphic representation of survival rate after resection in authors' series of pulmonary malignancy.

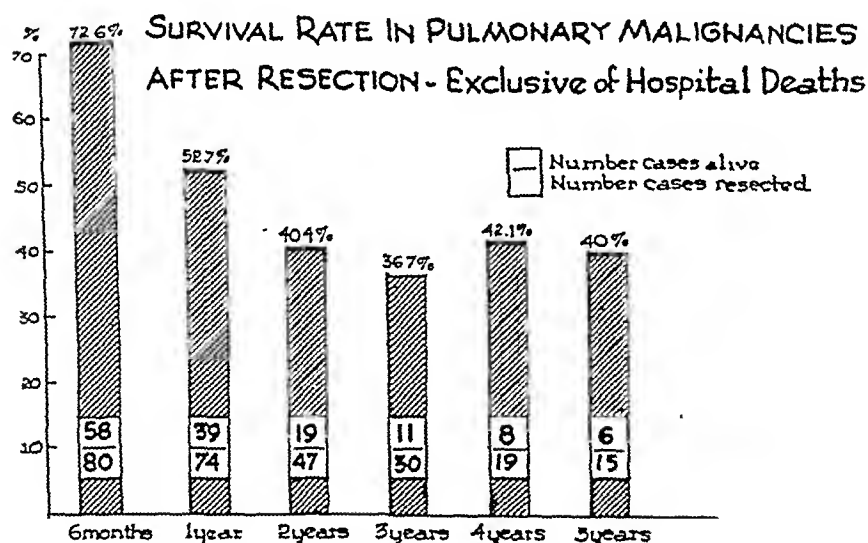


CHART 20.—Graphic representation of survival rate after resection, exclusive of hospital deaths in authors' series of pulmonary malignancy.

the survival-times on the basis of the studies reported herewith, so that the relative merits of the two procedures might be evaluated on the most essential of all criteria, how long the patient lives.

Gross Survival Rate.—Of the 107 patients operated upon six months, or more, ago (Chart 19), only a little over half (58) survived the first six-month period after operation. The 49 deaths within this period, however, include 27

SURVIVAL RATES IN PULMONARY MALIGNANCIES AFTER RESECTION According to Extension and Localization of Lesion

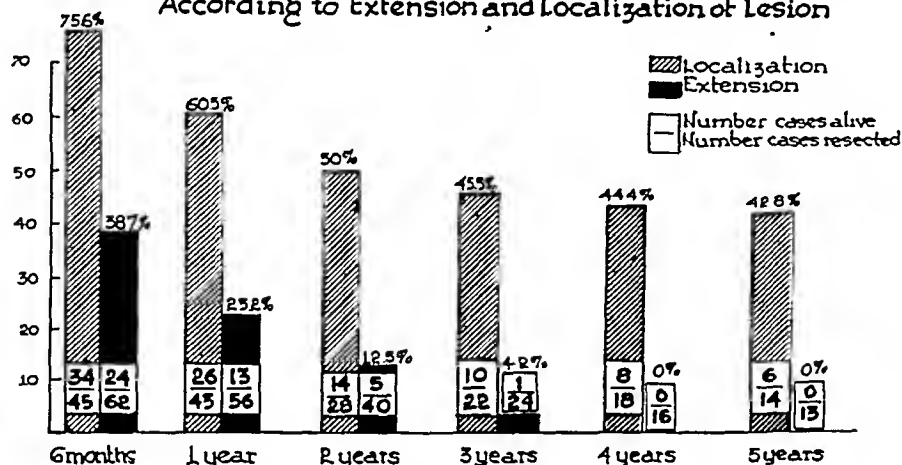


CHART 21.—Graphic representation of survival rate after resection according to extension and localization of lesion in authors' series of pulmonary malignancy.

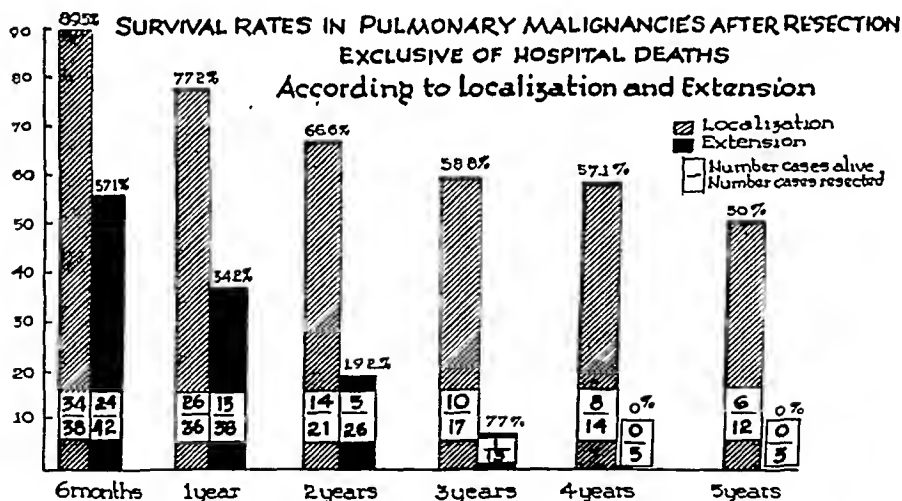


CHART 22.—Graphic representation of survival rate after resection exclusive of hospital deaths according to localization and extension of lesion in authors' series of pulmonary malignancy.

deaths which occurred in the hospital immediately after operation. Approximately three-fifths of the patients, again including those who died in the hospital, died within the first year. After that time, however, the rate of death increases very much less rapidly, and by the end of five years approximately

a fifth of all the patients submitted to resection were still alive. To express it differently, the distribution curve for the survival rate drops rather rapidly within the first year after operation, but by the third year has been stabilized and continues almost as a plateau until the fifth year. The assumption seems reasonable that a patient who lives through the third year after operation has a good chance of being alive at the end of five years. At the present time three patients are alive in the fifth year after operation and one each in the sixth and the tenth year after operation.

When the survival rate is calculated on the basis of the patients who left the hospital alive after surgery, those who died in hospital being excluded (Chart 20), the distribution curve is similar to the curve just described but is

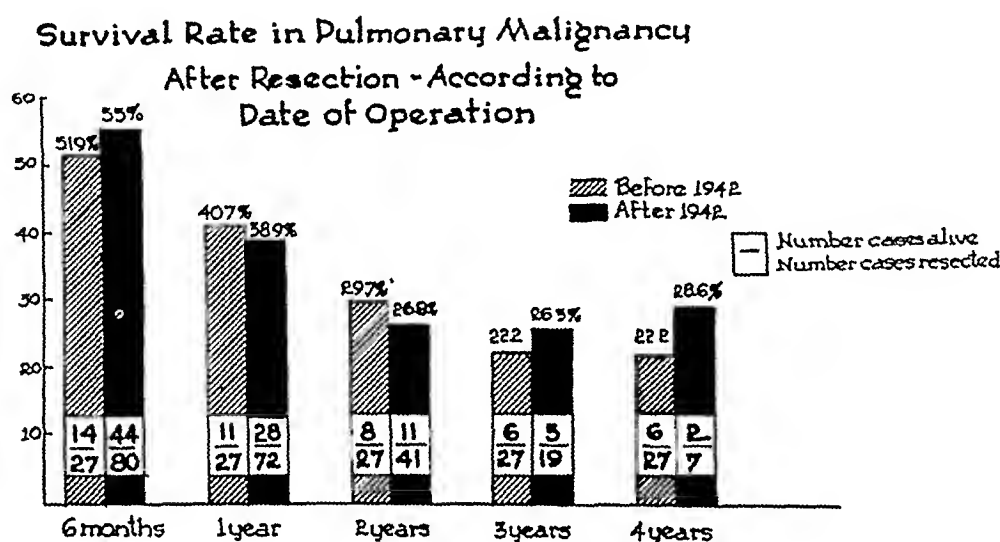


CHART 23.—Graphic representation of survival rate after resection according to date of operation in authors' series of pulmonary malignancy.

considerably more encouraging, the survival rate at the end of five years reaching 40 per cent, against 22 per cent when all patients are included.

Survival Rate According to Status of Growth.—Of all the factors which might affect the survival rate in carcinoma of the lung the most obvious is the status of the growth, as determined at operation and by pathologic study of the resected specimen. The 107 cases in which operation was performed six months, or more, ago were, therefore, analyzed from the standpoint of whether the growth was limited to the lung or had extended beyond it by encroachment upon contiguous structures or by regional metastases (Chart 21). As might have been expected, the survival rate was significantly greater among the patients whose growths were localized, no patient with extension at operation surviving beyond the three-year period, whereas the survival rate among patients with localized growths was 42.8 per cent at the end of five years. The curve is substantially the same when it is calculated on the basis of only the patients who left the hospital alive (Chart 22), the survival rate

among these patients with localized growths being 50 per cent at the end of five years.

Survival Rate in Relation to Date of Operation.—As already noted (Chart 15), the hospital mortality of pulmonary resection for carcinoma of the lung showed a distinct improvement after 1942, as compared with the mortality prior to that period, the improvement being attributed to improvements in technic and in preoperative and postoperative care. In an effort to determine whether the survival rate reflected the same improvement when analyzed

SURVIVAL RATE IN PULMONARY MALIGNANCY AFTER RESECTION
Exclusive of Hospital Deaths
According to Date of Operation

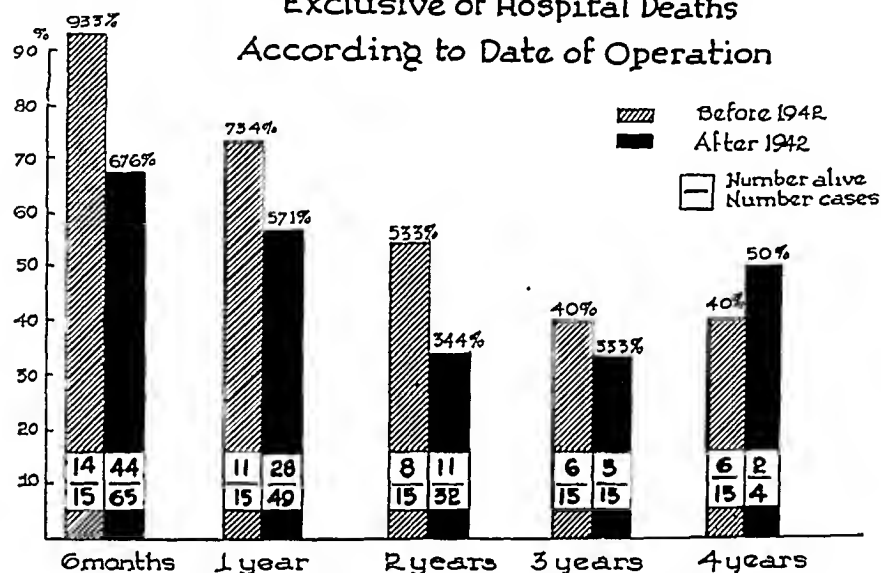


CHART 24.—Graphic representation of survival rate after resection, exclusive of hospital deaths, according to date of operation in authors' series of pulmonary malignancy.

according to the time at which operation was performed, the localized and nonlocalized cases were considered from this standpoint. When the group is analyzed as a whole (Chart 23), no significant differences are noted in the rates of survival before and after 1942. Even when the deaths in hospital are excluded (Chart 24), no great differences are observed. When the material is divided into localized (Chart 25) and nonlocalized (Chart 26) cases, the differences already commented upon in survival rates are once more apparent. In addition, there is small improvement in the survival rates for patients with nonlocalized growths after 1942, which perhaps reflects the better care, technically and otherwise, all patients received after that date.

No matter how the calculations are made, it is evident that the patient with a localized growth has, as, of course, might be expected, a much better chance of surviving for a considerable period of time after operation than has the patient with a nonlocalized growth. His chances are naturally influenced

by the type of care he receives, but the important consideration is that he is seen early, so that complete removal of the lesion is possible and can be achieved without undue risk at operation.

Actual and Possible Survival Rates.—The analysis of this series of 129 cases of carcinoma of the lung in which resection was done is discouraging from the standpoint of absolute figures. Five years after operation 21 of the 27 patients operated upon, who could have survived this period of time, had died. The figures are less discouraging, however, when it is recalled that without operation all of them would inevitably have died, and that all of them would have been denied the longer or shorter period of postoperative health

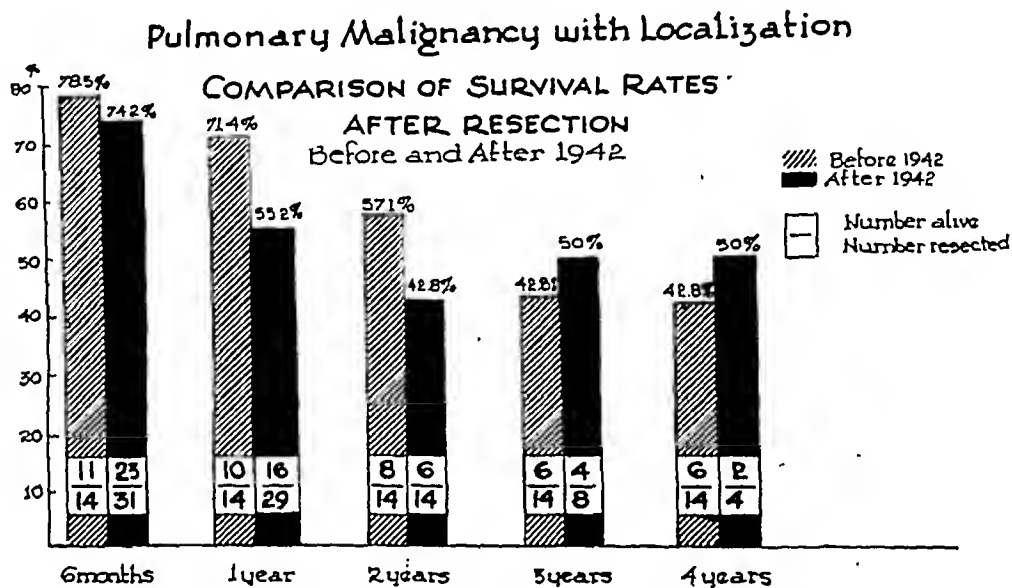


CHART 25.—Graphic representation of survival rate after resection according to date of operation in authors' series of pulmonary malignancy with localized lesion.

which many of those who eventually died did enjoy. Furthermore, the analysis of this series of cases clearly indicates what can be achieved in favorable cases, that is, the patients who are seen early enough to permit resection of the growth. At the present time (Chart 27), of every 25 clinical cases of carcinoma of the lung only nine are resectable, and of those nine, only two patients survive five years, or more. If every patient could be seen early enough to permit resection—a difficult but not necessarily an impossible goal—between five and six would survive five years, or more. There is no good reason why we should not at least set our sights to achieve such a result.

SUMMARY AND CONCLUSIONS

During the almost 11-year period ending December 1, 1946, 360 patients with carcinoma of the lung were observed, of whom 129 were submitted to pulmonary resection. The 129 resected cases are analyzed from the various standpoints, with special emphasis on diagnostic considerations and on sur-

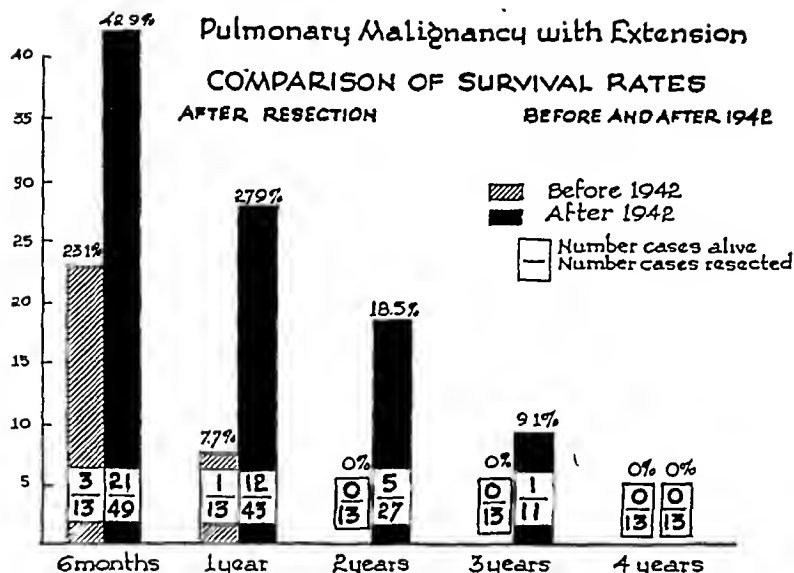


CHART 26.—Graphic representation of survival rate after resection according to date of operation in authors' series of pulmonary malignancy with extension of lesion.

SURVIVAL EXPECTANCY IN PULMONARY MALIGNANCY

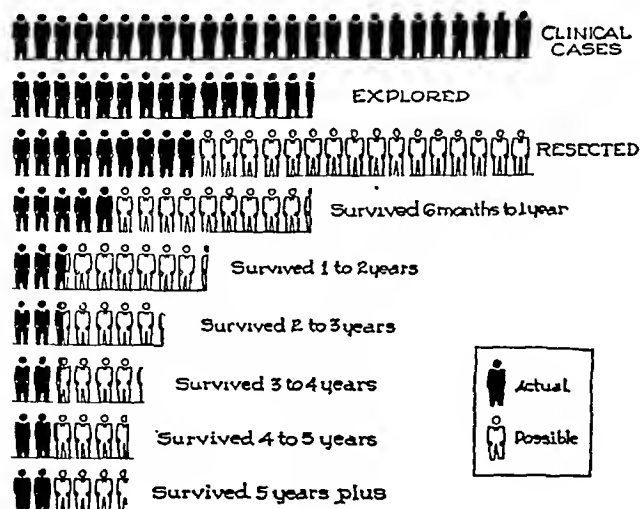


CHART 27.—Schematic representation of actual survival expectancy in pulmonary malignancy based upon present experience (in black) and of possible survival expectancy if all cases were diagnosed early enough to permit resection.

vival rates. In most respects the data in this series bears out the data reported by other observers.

The key to early diagnosis is the recollection of the possibility of the disease in all patients with symptoms referable to the chest, particularly those over 40 years of age. Routine roentgenologic examination is the most valuable of all diagnostic methods. It should be supplemented as indicated by bronchography, bronchoscopy and biopsy, aspiration of expectorated material or of material aspirated at bronchoscopy, and, if the diagnosis cannot otherwise be arrived at, by exploratory thoracotomy.

The incidence of operability in carcinoma of the lung remains discouragingly low. The surgical mortality has shown progressive improvement and is not high if it is remembered that the mortality of the disease in the absence of operation is 100 per cent.

The immediate surgical mortality is caused by a certain proportion of preventable errors, but the incidence of cardiovascular complications, which are not usually preventable, is high, and the risk must be assumed if patients likely to develop them are not denied their chance of salvage.

An analysis of all patients in the series operated upon six months, or more, ago indicates that a patient who lives through the third year after operation has a good chance of being alive at the end of five years. The survival rate is significantly greater in patients whose growth was localized, no patient with extension at operation having survived beyond the three-year period. Every calculation, regardless of the standpoint from which it is made, indicates that while the patient's chances of survival are influenced by the type of care he receives, the important consideration is that he is seen early, so that complete removal of his lesion is possible and can be achieved without undue risk at operation.

REFERENCES

- ¹ Adams, Ralph: Primary Lung Tumors. *J. A. M. A.*, 130, 547-553, March 2, 1946.
- ² Brock, R. C.: Surgical Treatment of Bronchial Carcinoma. *Brit. M. J.*, 2, 257-259, August 28, 1943.
- ³ Brock, R. C.: Carcinoma of the Lung. *Brit. J. of Radiology*, 17, 102-105, 1944.
- ⁴ Burnett, W. E.: Discussion of article by Gebauer, P.: Differentiation of Bronchiogenic Carcinomas. *J. Thoracic Surg.*, 10, 395, 1940-41.
- ⁵ Cames, Oscar J., Cesanelli, Alfredo, and Tricerri, Fernando E.: Clinical Experience in the Surgical Treatment of Cancer of the Lung. *La Prensa Medica Argentina*, 33, 1621, August 9, 1946.
- ⁶ Churchill, Edward D.: Resection of the Lung, *Surgery*, 8, 961-991, 1940.
- ⁷ Clagett, O. Theron, and Brindley, G. V. Jr.: Bronchogenic Carcinoma. *Surg. Clin. of N. Amer.*, pp. 839-849, August, 1944.
- ⁸ Dolley, F. S., and Jones, J. C.: Lobectomy and Pneumonectomy for Lung Suppuration and Malignancy. *Journal-Lancet*, 59, 162, 268, 1939.
- ⁹ Edwards, Tudor: Carcinoma of the Bronchus, XIeme Congres de la Societe Internat. de Chirurgie, 2, 529-534, Bruxelles, 1938.
- ¹⁰ Fetter, Ferdinand: Carcinoma of the Lung: A Review of 31 Proved Cases at the Philadelphia Naval Hospital. *Ann. Int. Med.*, 18, 978-987, 1943.
- ¹¹ Graham, Evarts A.: Discussion of article by Lindskog: Bronchiogenic Carcinoma. *ANNALS OF SURGERY*, 124, 672, October, 1946.

- ¹² Linds kog, Gustaf E.: Bronchiogenic Carcinoma. ANNALS OF SURGERY, 124, 667-672, October, 1946.
- ¹³ Ochsner, Alton and DeBa key, Michael E.: Primary Pulmonary Malignancy: Treatment by Total Pneumonectomy: Analysis of 79 Collected Cases and Presentation of Seven Personal Cases. Surg., Gynec., and Obstet., 68, 435-451, February 15, 1939.
- ¹⁴ Ochsner, Alton and DeBa key, Michael: Surgical Considerations of Primary Carcinoma of the Lung: Review of the Literature and Report of 19 Cases. Surgery, 8, 992-1023, December, 1940.
- ¹⁵ Ochsner, Alton, and DeBa key, Michael: Carcinoma of the Lung. Arch. of Surg., 42, 209-258, February, 1941.
- ¹⁶ Ochsner, Alton and DeBa key, Michael: Carcinoma of the Lung. N. O. Med. and Surg. J., 93, 387, 1941.
- ¹⁷ Ochsner, Alton and DeBa key, Michael: Significance of Metastasis in Primary Carcinoma of the Lung. J. Thoracic Surg., 11, 357-387, April, 1942.
- ¹⁸ Ochsner, Alton, Dixon, J. Leonard, and DeBa key, Michael: Primary Bronchiogenic Carcinoma: An Analysis of 190 Cases, 58 of which were Successfully Treated by Pneumonectomy: A Review of the Literature. Clinics, 3, 1187-1245, 1945.
- ¹⁹ Ochsner, Alton, Dixon, J. L., and DeBa key, Michael: Primary Bronchiogenic Carcinoma. Dis. of the Chest, 11, 3, 1945.
- ²⁰ Overholt, Richard H.: A Common Masquerading Lung Disease. Dis. of the Chest, 9, 197-211, May-June, 1943.
- ²¹ Rienhoff, William F.: The Present Status of the Surgical Treatment of Primary Carcinoma of the Lung. J. A. M. A., 126, 1123-1128, December 30, 1944.

1430 Tulane Ave.
New Orleans 13, La.

THE PRESENT STATUS OF THE SURGICAL TREATMENT OF CARCINOMA OF THE LUNG*

WILLIAM FRANCIS RIENHOFF, JR., M.D.

BALTIMORE, MARYLAND

THIRTEEN YEARS have now elapsed since the first total pneumonectomy was performed in the Johns Hopkins Hospital. Previous to that time a diagnosis of pulmonary malignancy was made infrequently and more for academic than practical reasons. Prior to this time no therapeutic measures or methods were available which offered the patient more than palliation. Medicinal and radiation therapy were then, as now, equally ineffective and the disease when so treated was, and is, always fatal.

The surgical treatment of malignant tumors of the lung has been a boon to patients and a lively stimulus to clinicians interested in pulmonary lesions. Because of this increased interest on the part of physicians the diagnosis of tumors of the lung is made much more frequently than in the past, with the result that a greater number of such patients are being referred for operation. In a Medical Center in which a special interest in this type of surgery has been manifested, what seems a disproportionate increase in the frequency of these cases is apt to occur, but it may probably be true that the incidence of primary pulmonary cancer is on the increase.

It is the purpose of this report to record the clinical analysis, preoperative preparation, operative procedure, immediate and remote postoperative results in a series of 327 consecutive cases of carcinoma of the lung which have been referred for surgical treatment, not accounting for those instances in which the patient was obviously inoperable from the standpoint of the clinical findings.

CLINICAL ANALYSIS

Etiology.—Although the etiologic factors involved in the production of cancer are unknown, there is enough data accumulated to draw some conclusion as to the influence of certain factors to which human beings are exposed. In this and other series of cases reported, one fact has been outstanding as probably playing a definite rôle in the production of pulmonary carcinoma, that is the great majority of patients afflicted with this malady are residents of urban districts. In such districts, from the cradle to the grave, the lungs are constantly exposed to many irritating substances, such as dust, dirt, various fumes, gases and other atmospheric pollutions which have a deleterious effect on the lining cells of the bronchial tree throughout its entire extent. It is a well-known fact that miners and, particularly in various places in the world,

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

laborers exposed to certain foreign particles in the air, are very prone to develop growths in the lung. It is also fully recognized that individuals who are working in contact with irritating gases, such as chlorine and others, frequently develop epithelial growths in the air passages. Changes in oxygen tension will affect the type of epithelial lining cells, often causing a metaplasia from the cylindrical cell to a flat cell. This morphologic transposition may also be found in the bronchi which are tributaries to areas of infection, such as lung abscess or bronchiectasis. In other words, chronic irritation, regardless of the type, will produce changes in the growth-rate and shape of the cells of the lung which seem to be very sensitive to this pollution of the atmosphere. It will be interesting, now that women are smoking, to see if the much higher ratio of the malignancy of the lung in men, is decreased by an increase in the incidence in women.

Due to the occupational hazards mentioned above as well as habits, a higher incidence of primary malignant tumors of the lung is to be expected in the male than in the female. Table I shows the distribution according to sex of the patients in this series. It is to be noted that there is a much higher incidence in the male than in the female, a ratio of almost 6 to 1 in favor of the males. The incidence of involvement of the right and left sides is approximately the same.

In regard to the age incidence of primary malignant tumors of the lung, this does not vary to any great extent from the age incidence of malignant growths elsewhere in the body. The majority of the patients were in the fourth to sixth decades. Perhaps patients in the second to fourth decades were more frequently affected than would be the case of other viscera; however, this series of cases, although relatively large, is far too small to warrant an exact statement. Twelve of the cases fall into the sixth decade. The oldest patient in this series to be operated upon was 76 years of age and the youngest 19. Age, in itself, seems to offer no contraindication to operation. Not infrequently an older patient from a physiologic point of view is a far better operative risk than a younger one. In this series the older patients were surprisingly unaffected by the operative procedure, including the patient age 76, and generally had uneventful postoperative convalescences. Pulmonary cancer, however, generally speaking, is a disease of advanced age.

Unfortunately for the lay public, physicians as a whole, because of the lack of therapeutic measures to combat such lesions or to effectively treat them, have been less acutely interested in the possibility of malignant growths of the lung than those of other viscera or organs of the body. It is, therefore, important that not only all physicians, but also the lay public, should become cognizant of their respiratory tracts in order that they may at the earliest moment seek confirmation or dissipation of their apprehensions in regard to signs and symptoms originating in their respiratory organs.

It is mandatory that the knowledge of the signs and symptoms originating as a result of malignant tumors of the lung be made known to the public as a whole, just as every woman knows the significance of a tumor of the breast

CARCINOMA OF LUNG

and realizes the importance of immediately consulting a physician concerning such a tumor.

In the analysis of this series of patients herein reported, in regard to the most frequent signs and symptoms occurring in such cases of primary cancer of the lung, only those signs and symptoms were included that could be attributed to involvement of the lung itself and not to invasion of contiguous structures or distant metastases. In 71 per cent of the patients in this series cough was the chief symptom. In a nation of heavy cigarette smokers, in which the population supplying the majority of patients breathes the polluted atmosphere of cities, cough is almost universal and is due mainly to nonspecific irritation of the respiratory tract. The important point about coughing that should make one suspicious of the presence of an intrabronchial growth is the departure from the normal for any individual. If in an adult "chronic cough"

TABLE I
DISTRIBUTION ACCORDING TO SEX OF CASES OF
PRIMARY CARCINOMA OF THE LUNG

	Operable	Inoperable
Male.....	84%	86%
Female.....	16%	14%

TABLE II
SIGNS AND SYMPTOMS OF CARCINOMA OF THE LUNG

Cough.....	71%
Hemoptysis.....	63%
Pain.....	50%
Loss of weight.....	39%
Hyperpnea.....	23%
Pneumonitis.....	18%
Fever.....	13%
Tightness in chest.....	3%

the type of cough changes to a spasmodic, productive or nocturnal type, or, again, if a person who has heretofore coughed infrequently suddenly begins to be annoyed by a hacking cough day and night, attention should be focused on the bronchial tree and the presence of a bronchial neoplasm should be suspected. The development of a cough or changes in the character of coughing can portend an extremely serious condition. Until physicians as a whole, as well as the lay public, become more acutely aware of the serious significance of this sign, the opportunity for early and satisfactory treatment of pulmonary neoplasms will be denied to many patients. It is to be noted, again, that the outcome in this condition, unless recourse is had to surgery, is invariably fatal. These symptoms and signs are listed according to the frequency of their occurrence in Table II.

In 63 per cent of our patients expectoration of blood or hemoptysis was associated with coughing. This varied from streaking of the sputum to the

expectoration of large and copious amounts of blood, up to six ounces (180 cc.). In the latter group the accumulation of blood in the mouth was preceded by a "gurgling" in the chest on one side which warned the patient of the impending hemoptysis. In our experience, copious hemoptysis has usually been associated with the adenocarcinoma type of intrabronchial growth. Unless

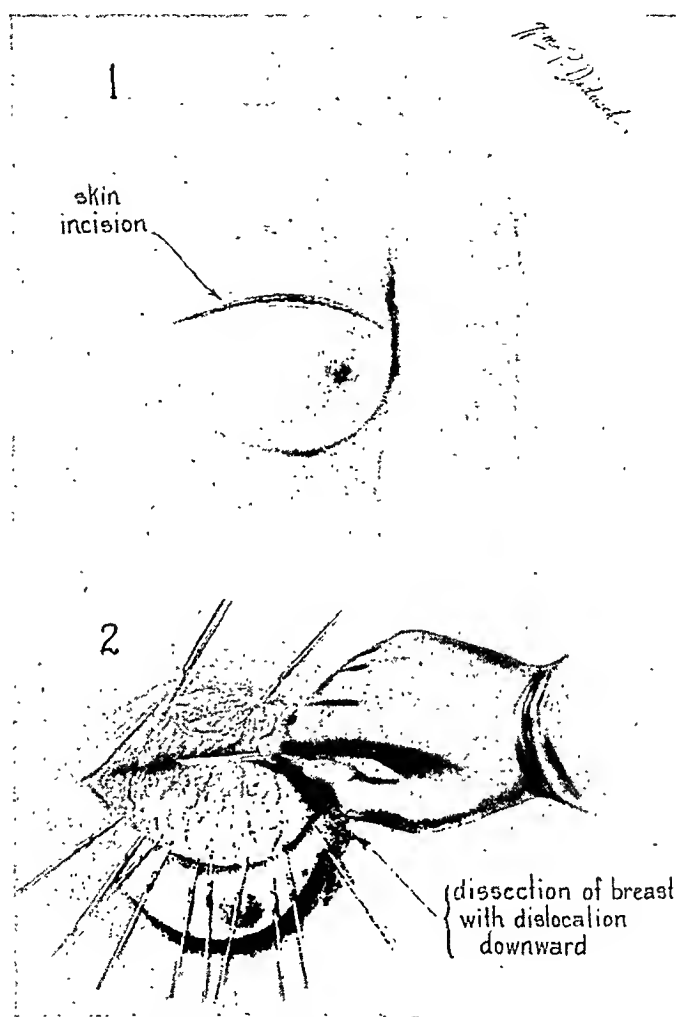


FIG. 1.—Demonstrating the first two operative steps using the anterior approach.

the roentgenograms and sputum examination are indisputably those of tuberculosis or bronchiectasis, hemoptysis must be considered to be due to an intra-bronchial growth until this has been ruled out by the many types of examinations at our command. The burden of proof is on the physician who, in any given case, states that hemoptysis is not due to a tumor of the lung. This is true even though a small number of tubercle bacilli may be present in the sputum. Tuberculosis and cancer may be associated, and were in four cases

in our series. Clinical examinations to diagnose an intrabronchial tumor in no way interfere with the treatment of pulmonary tuberculosis; but if a patient bleeding from a tumor of the lung is observed for months in an attempt to prove the case to be tuberculosis, in many instances he will have lost his only opportunity for successful treatment. The discovery that the bleeding was originally from a neoplasm will have come too late.

Although it is uncommon to have pain as a prominent symptom in cancer of other organs, it is third in prominence among the signs and symptoms in patients afflicted with cancer of the lung. Pain arising from an intrabronchial neoplasm must be differentiated from the pain due to direct invasion of contiguous structures. Pain arising from the lung itself is not associated with the respiratory cycle, as is the pain of pleuritis. It is most often described by the patient as a constant dull ache deep in the chest. The frequency with which the actual position of the tumor, as shown by roentgenography, coincided with the location of the level of pain on the chest wall, as indicated by the patient, was surprising. In all probability pain does not arise within the tumor itself but is a result of pressure on the bronchial wall. Persistent pain in the chest, in the absence of inflammatory disease or aspiration of a foreign body, should always lead to careful investigation of the respiratory tract. Pain down the arm or in the chest wall, so characteristically found in the so-called "superior sulcus or Pancoast tumor," is, as a rule, due to direct invasion of the ribs or the brachial plexus or both. This distribution of pain is considered a very unfavorable symptom from the standpoint of operability.

Loss of weight due to cachexia in advanced carcinoma of any organ in the body, particularly the gastro-intestinal tract, is well-known and obvious; but not so easily understood was a striking loss of weight in 39 per cent of the cases of pulmonary carcinoma. This loss of weight was, of course, due in part to coughing, loss of appetite because of hemoptysis and sputum, worry, *etc.*; but the rapid gain of 30 to 50 pounds in a few months after total pneumonectomy for the removal of a relatively small growth remains unexplained.

Fifth on the list of signs and symptoms is hyperpnea, occurring in 23 per cent of the patients. These patients complained of a sudden desire to breathe in deeper breaths, not exactly similar to air hunger but approximating this condition. The deep breathing sensation one experiences when breathing carbon dioxide would seem to be similar. This paroxysmal hyperpnea came on suddenly and lasted for a few seconds or a few hours. The mechanism for this respiratory phenomenon is difficult to explain. It may possibly be caused by a plug of mucus occluding a secondary or tertiary bronchus already partly plugged by an intrabronchial neoplasm, the bronchopulmonary segment of lung, to which the occluded bronchus is a tributary, thus, becoming the site of an obstructive emphysema. Reflex disturbances in the respiratory rate and amplitude are thus set up. With expulsion of the mucus plug the respiratory rate returns to normal. Such unusual changes in the respiratory cycle, even though of short duration, should excite one's curiosity sufficiently to suggest a thorough examination of the bronchial tree.

Eighteen per cent of the patients had suffered from attacks of pneumonitis associated with episodes of fever and all the signs and symptoms characteristic of pneumonia. It was frequently possible to obtain a history of numerous attacks of so-called "pneumonia" in the recent past. The chief characteristic of these attacks was that they occurred at any time of the year, with apparently no tendency toward seasonal incidence, as in the true epidemic pneumonia.

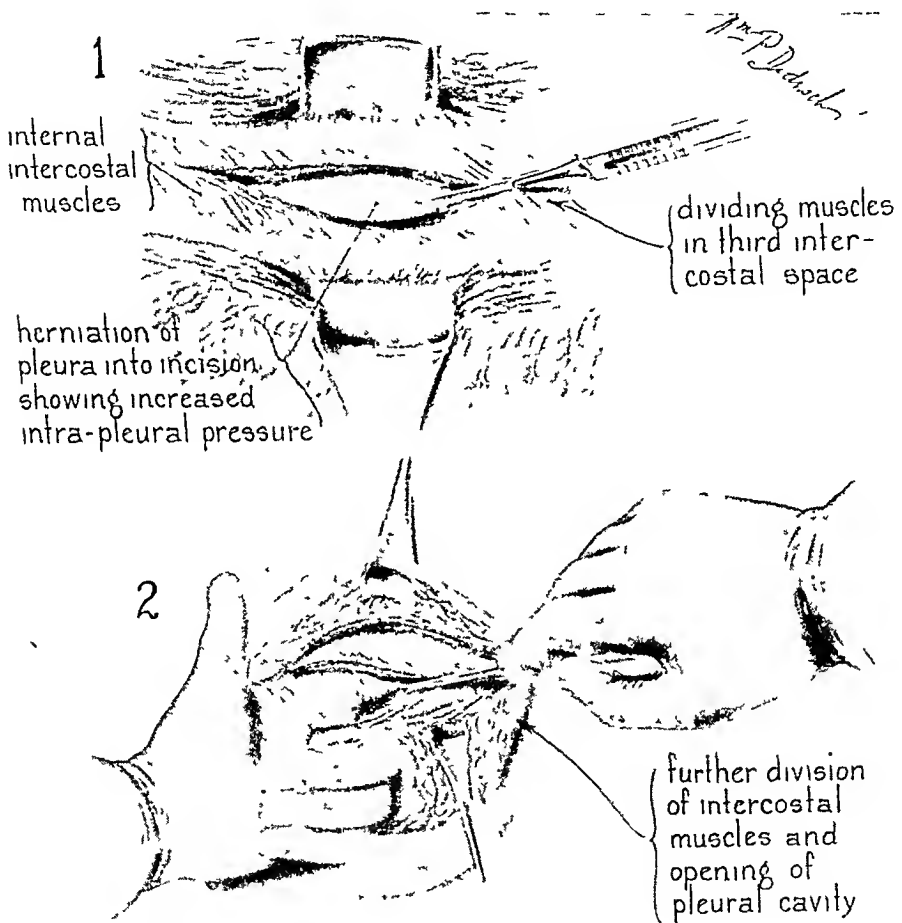


FIG. 2.—Showing entrance to thoracic cavity with minimum amount of damage.

Furthermore, physical signs were atypical and in unusual locations as regards the lung itself. Lobar, broncho or interstitial pneumonia, as a rule, present fairly typical physical signs. This is not the case in pneumonitis due to bronchial obstruction associated with primary carcinoma of the lung. The explanation for these unusual observations is not far to seek when their pathogenesis is considered. When obstruction of a bronchus, whether primary, secondary, tertiary or quaternary occurs as a result of a new growth, alone or in

association with a mucus plug, the bronchial tree peripheral to the point of occlusion becomes filled with mucus. Eventually infection of this bronchopulmonary segment occurs and the clinical syndrome of localized pneumonitis is produced. A portion of a lobe of greater or lesser dimensions, the entire lobe or even the entire lung may be involved. If exacerbations of such a pneumonitis are of sufficient frequency, bronchiectasis, or even an abscess, will at times supervene. Often such an abscess perforates into the pleura and produces putrefaction empyema. The point to be emphasized is that when such an unusual sequence of events takes place, or when any one of the previously-mentioned inflammatory episodes occurs that cannot be explained as a complication of a typical pneumonia or as a result of aspiration of a foreign body, an intrabronchial growth should be suspected. It is the repetitious nature of such pneumonitis which makes it so significant.

In general, it may be stated that there are no characteristic or pathognomonic signs and symptoms of primary carcinoma of the lung. This lesion masquerades as many of the more common disorders of the lung. The onset is often insidious, but the recurrent nature of signs and symptoms previously described should call attention of the patient and the physician to the respiratory tract so that a thorough examination will be carried out. Especially is this true of a patient who has previously had excellent health and in whom, after the second decade, there develops a cough associated with spitting of blood. Too often precious time is lost because of a diagnosis of pulmonary tuberculosis, lung abscess, unresolved pneumonia, bronchiectasis or heart disease. The methods of examination employed to rule out the presence of an intrabronchial growth in no way interferes with the diagnosis or treatment of any of the conditions which are at times mistaken for such a growth.

Diagnosis.—In this series of 327 cases the roentgenograms of the chest were positive in every instance. It is not suggested that a diagnosis of primary carcinoma of the lung could be made from the roentgenographic studies alone, but there was in each case an abnormal shadow which necessitated further study and examination. Thus, it may be stated emphatically that in every instance in which roentgenograms of the chest show a departure from normal, and in which this departure is not in every way characteristic of one of the commoner lesions of the lung, the presence of bronchogenic cancer should be inferred. Unquestionably, the roentgenograms of the chest are the most important and simplest method of examination at our disposal. Even in the earliest stages of growth of a primary carcinoma of the lung the lesion, as a rule, can be discovered. In the early part of the last decade, and even today, it was, and is, disheartening to watch an early lesion develop over a period of months into an inoperable cancer of the lung because physicians who were not, and are not, aware of this danger would advise the patients to "wait and see what happens." "Coming events often cast their shadows before them"—it is equally true that shadows cast by hilar infiltration due to other conditions, such as tuberculosis and even normal structures, are confusing. However, an infiltrating hilar shadow in a patient past middle age, associated with cough,

hemoptysis and the absence of tubercle bacilli in the sputum almost certainly indicates a bronchogenic carcinoma; most of these carcinomas are located at or near the hilus or root of the lung. The diagnosis of cancer of any organ cannot be definitely made by roentgenologic examination alone, but the more experienced the observer the greater the likelihood of an accurate interpretation. Positive roentgenograms may show a shadow produced by the new growth itself or by an area of atelectasis, bronchiectasis, pneumonitis or abscess caused indirectly by occlusion, by the growth, of a bronchus leading to a bronchopulmonary segment or segments.

In my experience, second to the roentgenogram in importance in yielding information which is helpful in arriving at a definite diagnosis is bronchoscopy. In fact, either by direct vision or biopsy or both a positive diagnosis of primary carcinoma of the lung can be made only in this manner. In 70 per cent of the patients in this series a positive biopsy of the cancer was obtained. A pulmonary new growth in the periphery or even in the hilar lesions confined to the upper lobes may be beyond the vision of the bronchoscopist. Nevertheless, valuable information can be elicited by bronchoscopy even when the growth cannot be seen, such as fixation or deformity, or both, due to pressure of any visible portion of the bronchial tree. The presence of blood or purulent discharge from certain bronchi serve as a lead. In this series of cases there have been no untoward results during or after bronchoscopic examinations.

Bronchography is a useful diagnostic method only to reveal occlusion of a bronchus by a small growth which does not produce a shadow in the roentgenograms of the chest. However, it is a harmless procedure and may be the link in the chain of evidence pointing to the possible presence of carcinoma of the lung.

Aspiration biopsy has a limited field, is often difficult to interpret, and such procedures are not without danger of implanting some cells along the tract of the aspiration needle or infecting the pleural cavity with the same cells, with tubercle bacilli or other pyogenic organisms. Aspiration of the bronchial tree has in some instances revealed cancer cells which could be obtained for microscopic examination.

Exploratory thoracotomy should be resorted to far more frequently in the future than it has in the past. This is, with the present-day anesthetics and surgical technic, a relatively harmless procedure—far more so than exploratory celiotomy and attended with fewer dangerous sequelae, such as adhesions. Exploratory thoracotomy is far less incapacitating than celiotomy. When it has been impossible to arrive at a definite diagnosis by all the means at our disposal this procedure should be performed at once, if a dangerous pulmonary lesion such as primary carcinoma is suspected. In our series of cases no deaths have occurred as a result of simple exploration of the chest. If direct observation and palpation of the lesion does not reveal the true nature, excision of the entire area in the lobe should be performed for immediate microscopic examination, and the diagnosis is made as is customary for questionable cases of carcinoma of the breast. If further discussion of the sit-

CARCINOMA OF LUNG

uation with the patient seems advisable, the wound may be closed and the patient returned to his room for further consultation. Later in the week the chest can be reopened and the definite procedure carried out. The old idea that opening the thoracic cage at operation is another form of euthanasia must be abandoned. The impression that all primary malignant tumors of the lung are slow-growing and late in metastasizing is incorrect.

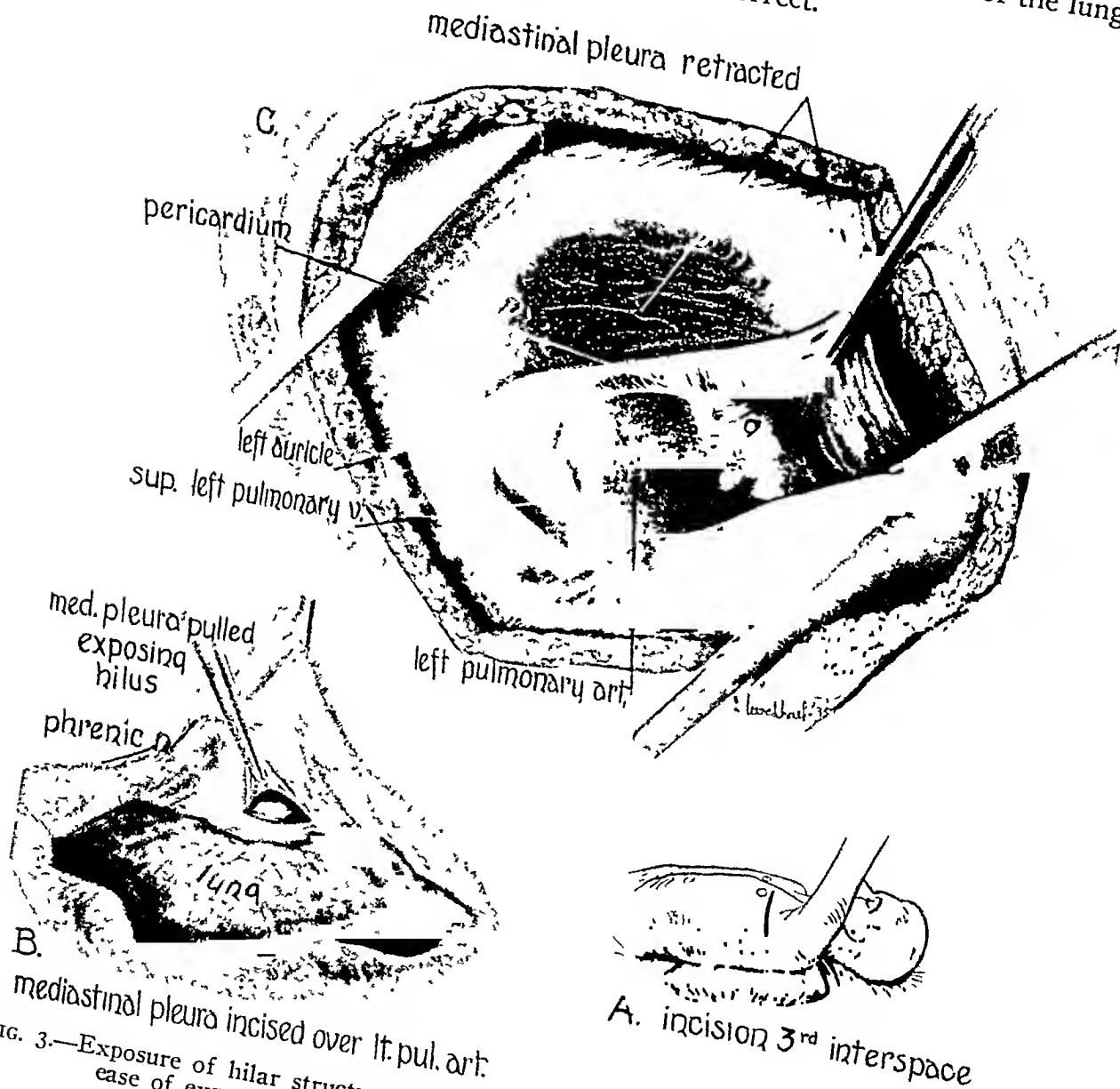


FIG. 3.—Exposure of hilar structures on the left side through anterior approach. Note ease of exposure of pulmonary artery, aorta and pulmonary veins.

Pathology.—The surgical removal of primary carcinoma of the lung in a relatively early stage has brought about changes in our ideas of the origin and nature of the growth of such tumors. In the past practically all the data were based on the autopsy in very late cases, when it was impossible on account of the almost universal involvement of the lung and contiguous structures to determine the nature, origin and progress of the growth within the lung. In this

series of cases the tumors occurred at or adjacent to the hilus, the minority in the periphery of the lung. The latter seemed to spread throughout the area of the lung in which they originated by centrifugal growth, most of them apparently having arisen in the alveolar lining cells. The hilar tumors, all of which were bronchogenic in origin, grew grossly in two separate fashions. The one, an intrabronchial tumor arising apparently from the bronchial mucosa, grew into the lumen of the bronchus and towards the trachea. The centripetal tendency of the growth, occluding completely or partly the primary or secondary

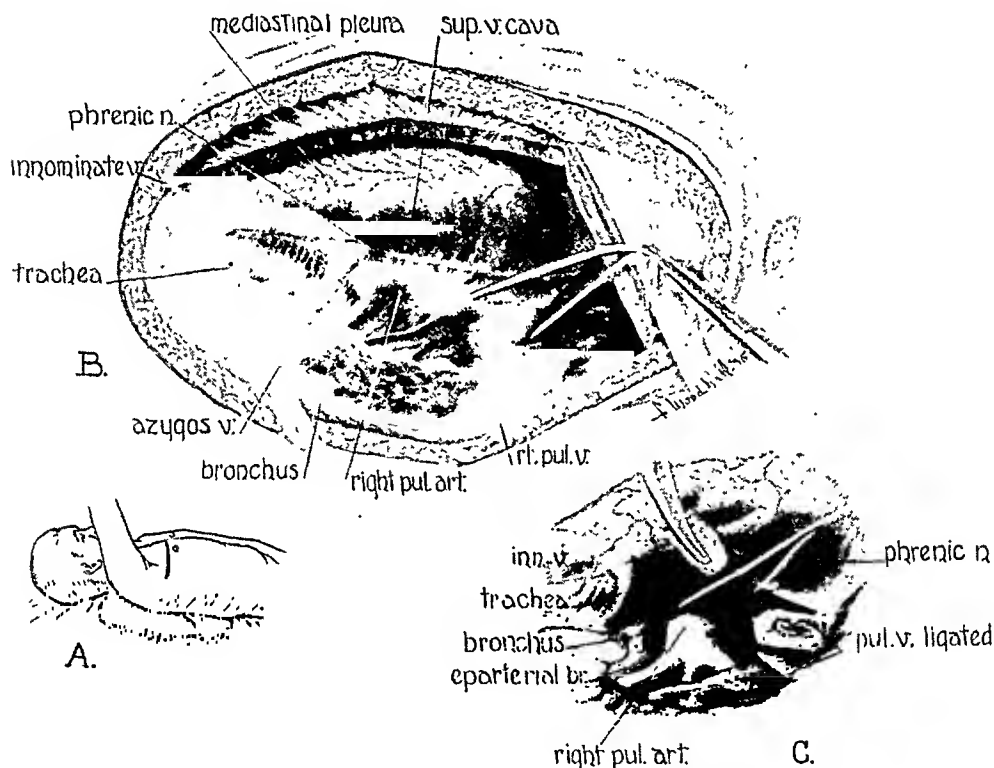


FIG. 4.—Exposure of hilar structures on right side. Pulmonary vessels lying anterior to bronchus are readily demonstrated.

bronchus was characteristic. The other type of hilar growth was an extra-bronchial tumor which, probably arising in the wall of a secondary, tertiary or quaternary bronchus, would break through the wall and grow along outside of, and often completely around, the bronchus. This type of growth, also, showed this centripetal tendency, growing around and about the secondary and primary bronchi and then spreading directly into the mediastinum to involve the structures contained therein.

The clinical course is dependent to a great extent on the method of growth. It is, of course, obvious that the intrabronchial type will produce respiratory difficulties, cough, sputum, and hemoptysis much earlier than the extra-bronchial tumor. The first symptoms caused by the latter method of growth may be, for example, interference with the venous return from the neck owing

to the involvement of the superior vena cava on the right side, or recurrent laryngeal palsy on the left, or Horner's syndrome. Malignant tumors arising in the periphery are, as a rule, asymptomatic. They may be said to arise in the silent area of the lung and as they do not, as a rule, produce bronchial obstruction or erode pulmonary vessels the symptoms and signs are usually those dependent on invasion of the pleura and chest wall and, by direct extension, the brachial plexus.

In 70 per cent of the 112 patients upon whom a total pneumonectomy was performed there were metastases to the bronchial and tracheal lymph nodes. This fact emphasized the necessity of performing a total pneumonectomy with dissection of these regional nodes in order to effect a permanent cure. In the remaining 215 cases that were inoperable, in addition to the metastases in the regional nodes the various organs and structures that were the site of metastases are listed in the order of the frequency of their involvement: supraclavicular and axillary lymph nodes, liver, pleura, pericardium and heart, contralateral lung, osseous tissue, brain and multiple areas in the skin and subcutaneous tissue.

The characteristic histologic structure of the tumor occurring in this series of cases was that of a flat and squamous cell carcinoma and adenocarcinoma. Under these two main headings were included various examples such as oat cell, cylindrical cell and adenocarcinoma thought to be different forms of the same tumor. The adenocarcinoma type is pleomorphic. Sections of the tumor differ depending upon the region from which they were cut. Sixty-five per cent of the cases in this series were composed of a flat or squamous cell cancer and 35 per cent the adenocarcinoma group.

It is interesting to note that the length of life, computed on the basis of the microscopic characteristics of the tumor, showed that those afflicted with the squamous, or flat cell type, lived a greater length of time than those with the adenocarcinoma type.

Treatment.—Preoperative Preparation: For several days preceding operation the patient should be carefully prepared. It has been our custom to treat the patient with intramuscular injection of penicillin 30,000 units, every three hours, avoiding awakening the patient at night. In addition to this penicillin aerosol should be employed. Whether or not some of the sulfonamides should be used has been questioned. It is my personal opinion that for some days, approximately three, sulfamerazine may be administered by mouth. The patients, thus, have a protective blood level of this drug which apparently does no harm. It is merely an added questionable merit and so far we have not been able to observe any demerits.

However, the preoperative preparation which we consider of the greatest importance is the induction of artificial pneumothorax. The advantage of this procedure has been proved over a period of years. In the first place, it must be considered a therapeutic test, particularly in individuals in the fifth or sixth decade in which there may be a certain degree of unrecognized emphysema. Removing the lung at operation without knowing whether or not the patient

can sufficiently oxygenate himself with the remaining lung may constitute a fatal error, and in the past we have experienced this tragic result. The ability of the remaining lung to function sufficiently for the needs of the patient can be established before operation is performed by merely collapsing the lung on the affected side. Various tests, such as oxygen saturation of the blood at body rest and during exercise of various degrees of intensity can be ascertained. For

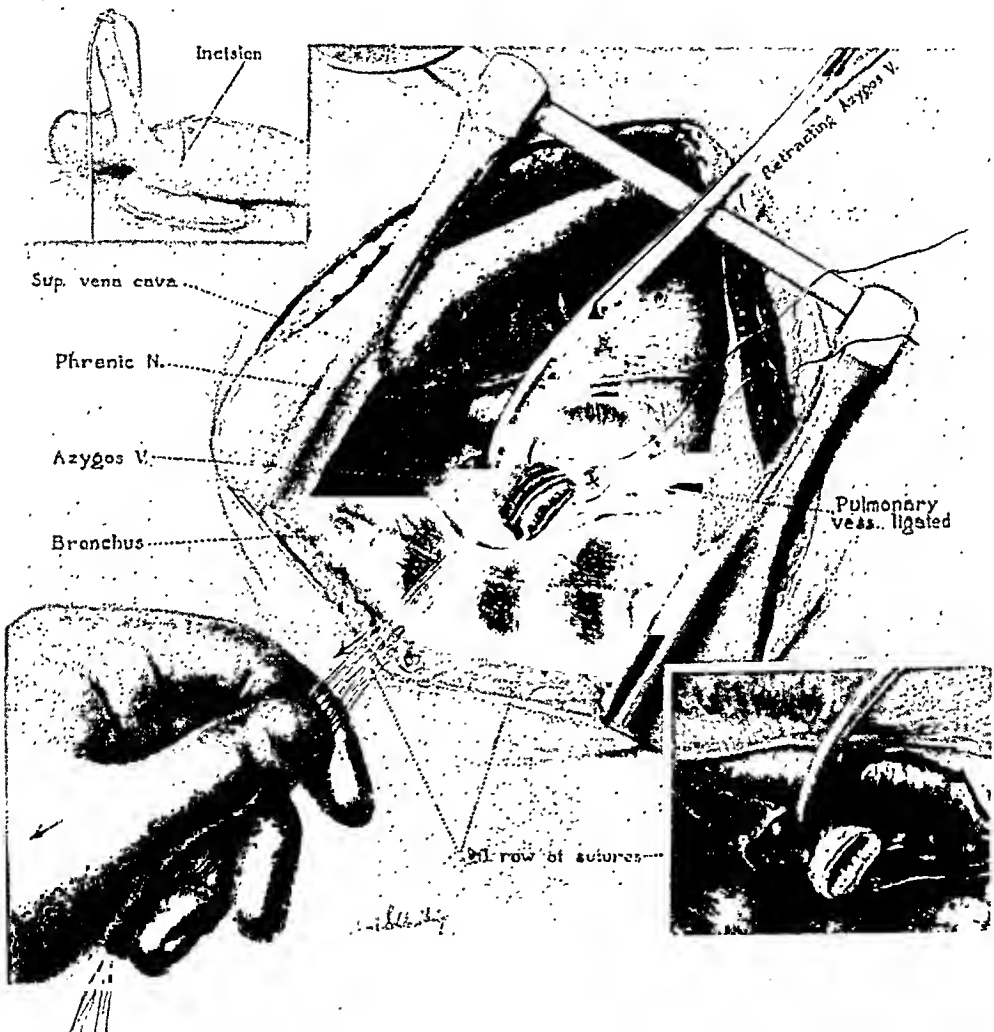


FIG. 5.—Demonstrating placing of interrupted mattress sutures occluding bronchus 1 cm. proximal to cut end. Note cuff-like portion of bronchus distal to suture line.

after all to cure a patient of a malignant tumor of the lung is futile, if the patient is left with insufficient aeration surface to support normal respiration. There are other minor advantages and secondary ones associated with artificial pneumothorax, such as diminishing the size of the lung so that the mechanical handling of this structure is technically made easier at the time of operation. Second, the patient has learned to breathe with one lung previous to operation

and with the increased intrapleural pressure, thus, avoids pleural shock on opening the thoracic cavity. Third, the blood flow through the collapsed lung is less than through the expanded contralateral lung and, therefore, the strain on the right heart from shifting greater blood flow through one pulmonary artery is graduated. Fourth, the location of a growth as regards the position relative to the mediastinum is often silhouetted and, therefore, located more accurately in the collapsed lung than with an expanded lung.

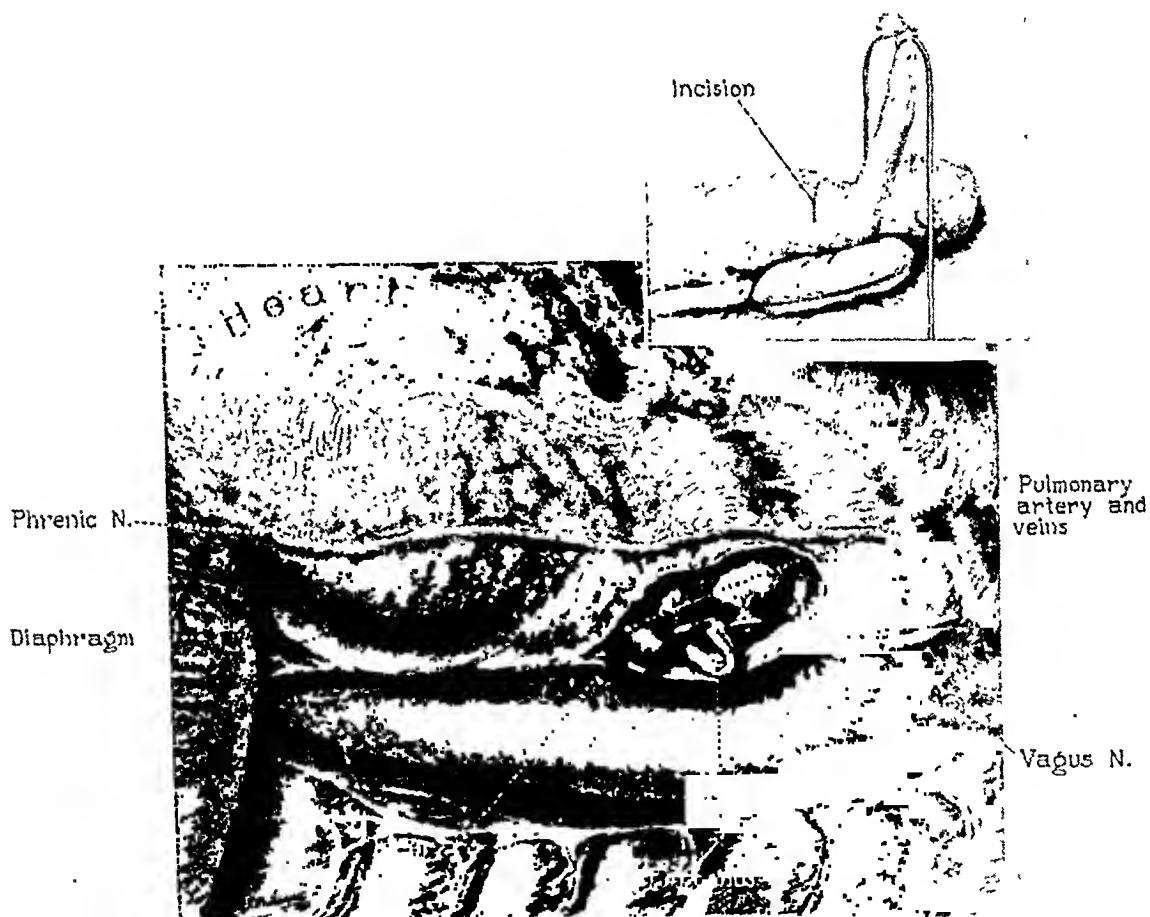


FIG. 6.—Lung amputated, hilar structures ready to be pleuralized, showing relation of pulmonary vessel to bronchus. Open cuff of bronchus visible.

Treatment.—In our present state of knowledge the only efficacious method for treatment of pulmonary carcinoma is by surgical removal of the entire organ, together with the regional lymph nodes. Medicinal and radiation therapy are only palliative, and as these tumors are, as a rule, radio-resistant, radiation therapy is of no benefit. It is interesting to note that in 215 cases of this series which were found to be inoperable at the time of exploration of the thoracic cavity, the average length of life after leaving the hospital was approximately five months, and this in spite of the fact that every type of supportive therapy, and in many instances, radiation therapy, were employed. It is to be emphasized again that the disease runs a fatal course in 100 per cent of the

patients in whom the lung cannot be removed in its entirety by operation. From an anatomic standpoint, the lung lends itself to surgical removal more readily than any other organ in the body, with the possible exception of the breast. From the point of view of the biologic characteristics of primary carcinoma of the lung surgical removal is more apt to be successful because of the relatively slow growth and spread of these tumors as compared to similar tumors in other regions of the body. Finally, the remarkable ability and tendency of the contralateral lung to undergo compensatory changes prevents incapacitation of the patient from a physiologic point of view.

{ OPERATIVE TECHNIC

The operative technic now employed for one-stage total pneumonectomy in the treatment of malignant tumors is essentially the same, except for closure of the bronchus, as that described by the author in 1933 in the Johns Hopkins Hospital Bulletin.¹

A number of points in the operative technic, as would be expected, are still controversial and as in any other operative procedure a unanimity of opinion as regards the various methods is hardly to be expected. But, after 13 years' experience and having employed this operative technic in 327 cases, of which 112 were total pneumonectomies, it is felt desirable, with the background of this experience to discuss certain steps in the operative procedure which are of special interest.

In the first place, the anterior approach is definitely to be preferred to the posterior or lateral for the following reasons: (a) the width of the intercostal spaces is greater anteriorly than posteriorly and the necessity for resection of ribs is, therefore, as a general rule, not necessary. This reduces the operative time and the general ill effects of the procedure upon the patients (Figs. 1 and 2). The thoracic cavity is more quickly entered with a minimum amount of damage to the chest wall and parietes. The use of a self-retaining retractor gives sufficient exposure so that the question of operability can be promptly judged. The time consumed from the incision to the entrance of the pleural cavity is far less when the anterior approach is employed, and associated with this there is a minimum loss of blood as well as trauma to tissues. If a greater amount of exposure is desired the adjacent intercostal cartilages can be incised and the ribs, usually the third and fourth, can be displaced cephalward or caudalward. Also, by slightly rotating the patient on the operating table, or the table itself, if desired, the incision can be extended laterally so that the maximum exposure can be obtained. If the tumor proves to be inoperable, the minimum of operative trauma has been incurred. The operability can be determined at once with the minimum operative effort. In the event the growth is operable the dissection of the hilar structures, such as the pulmonary artery and veins which lie anterior to the bronchus, is accomplished with far greater ease and facility when the anterior approach is employed (Figs. 3 and 4). The advantage of ligating the pulmonary artery at the beginning of the operation is obvious, the control of hemorrhage is, thus, more certainly

CARCINOMA OF LUNG

assured and the greater percentage of blood normally contained within the lung is returned to the general circulation *via* the pulmonary veins. Bleeding from any adhesions that may exist between the visceral and parietal pleura is reduced to a minimum. If for any reason it is felt desirable to interrupt the operative procedure and perform the operation in two stages, one can do so after ligation of the pulmonary artery, provided the pulmonary veins have been left intact. If the latter are ligated, the lobe which either one or both pulmonary veins drain, must be removed, for otherwise, gangrene of this portion of the lung will ensue. It is to be noted that the bronchial veins are vestigial in character and do not function sufficiently to even drain off the blood brought

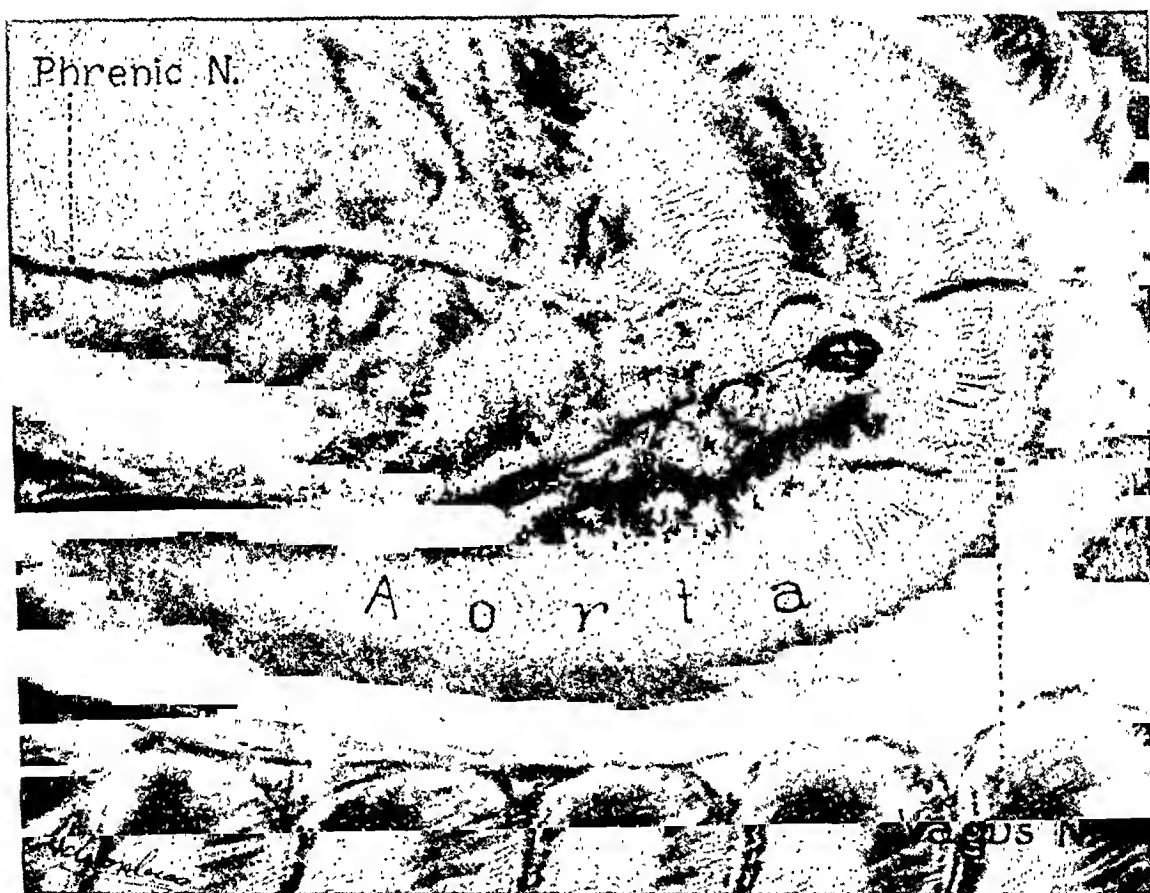


FIG. 7.—Left side of bronchus, plus denuded hilar surface covered with pleura.

to the lung by the bronchial artery, to say nothing of that from the much larger pulmonary artery. When the pulmonary artery, which carries venous blood is ligated collateral circulation through the bronchial artery is at once established. The bronchial artery brings sufficient arterial blood to the lung to maintain this organ in a normal state of nutrition and the circulation through the lung is, thus, changed from a venous to an arterial one. Whereas normally the greater amount of blood flowing through the lung capillaries is venous in character, originating from the pulmonary artery, the blood flowing into the same capillary bed from the bronchial artery is arterial. Stoppage of the blood flow from the pulmonary artery by ligation of the latter, incurs a great increase in

flow from the bronchial artery and, thus, fills the capillary bed in the lung and the branches of the pulmonary artery up to the point of ligation with arterial blood, containing such a high saturation of oxygen that the lung is, thus, rendered essentially functionless as far as further oxygenation of the blood flowing through it is concerned. The development of this collateral circulation *via* the bronchial artery begins after ligation of the pulmonary artery is performed. In the early days simultaneous ligation of one or both pulmonary veins invariably resulted in moist gangrene of the corresponding lobe or lobes because of the vestigial character of the bronchial veins. In the event of ligation of a pulmonary vein that portion of the lung whose venous bed is a tributary to that vein must be removed at the time of operation.

Not infrequently total pneumonectomy may be carried out with a greater degree of safety if a two-stage operation is performed, in which only the pulmonary artery is ligated as the principal objective of the first stage. This is particularly true when the lung is the site of a great deal of infection and extensively adherent. The arterialization of the lung with a flow of more highly oxygenated blood would appear to have a beneficial effect on the pulmonary infection and, therefore, the patient's clinical condition.* Dividing the operation into two stages greatly diminishes the shock of the procedure. It has been found that the pulmonary vessels, the artery and veins, are best ligated with silk, or cotton, and in no instance has this type of ligature been known to cut through the vessel wall.

TREATMENT OF THE BRONCHIAL STUMP

Since 1942, when the method of closing of the bronchus was first reported by the author in the ANNALS OF SURGERY² the bronchial stump has been occluded by the use of mattress sutures of interrupted silk or cotton placed through the bronchus in such a manner that the posterior membranous portion is approximated to the anterior cartilaginous wall, somewhat proximal to the end of the amputated stump, thus, creating a viable cuff from 1 to 2 cm. distal to the suture line which immediately fills with a fibrinous clot that thereafter becomes infiltrated with cells and eventually forms a fibrous plug (Fig. 5).

* In patients suffering from pulmonary tuberculosis ligation of the pulmonary artery has a definite deleterious effect. In eight patients the pulmonary artery was occluded with the idea of bringing about an atelectasis of the lung. The lesions were very extensive in each case and associated with large cavities. However, the change from a lower oxygen tension in the blood flow through the lung following ligation of the pulmonary artery, to the higher oxygen content of the blood flow from the bronchial artery exercised a most marked detrimental clinical and pathological effect on the patient and lung. This was apparent by a more rapid progression of the manifestation of the disease than would have been expected had the pulmonary circulation not been interfered with at all. No atelectasis was produced and cavitation increased rapidly. This unfavorable result was attributed to the fact that the tubercle bacillus flourished in an environment of higher oxygen content. It would be interesting to find out the effect of ligation of only the bronchial artery in pulmonary tuberculosis. The reverse condition of oxygen saturation would then obtain.

One of the more important steps in securing a satisfactory closure of the bronchial stump is to sew a pedicle flap of parietal pleura over the end of the stump of the bronchus approximating the pleura to the rim of the viable cuff. The use of any form of cauterization or traumatization to the end of the bronchial stump has been studiously avoided in order that agglutination of the rim of this cuff and the pleural membrane would be brought about immediately and permanently. Any foreign material such as sutures in the end of this cuff or devitalization of the rim of this cuff will militate against the immediate healing. Therefore, the bronchial stump should be sutured at least a centimeter



FIG. 8.—Right side of bronchus, plus denuded hilar surface covered with pleura.

proximal, if possible, to the point at which amputation is anticipated. Regardless of the type of suture material or the manner in which it is placed, cutting through the posterior or anterior membranous portion of the bronchus will frequently occur. This has been proved experimentally and at autopsy² (Fig. 6). Unless every opportunity is, therefore, afforded for the bronchial cuff distal to the suture line to heal by the formation of granulation tissue within its walls leakage will follow in a rather high percentage of cases. In the event that the bronchial growth extends up toward the carina, the bronchus and also the lower end of the trachea may be sutured after a diagonal incision in this structure has been made. This suture, as in the bronchus, should be tied sufficiently tight to approximate the walls of the bronchus or trachea, but not enough to cause crushing of the tissue. If so, the sutures will cut. They should also be

placed so that the knots are tied about the cartilaginous rings, that is on the anterior surface of the bronchus or trachea. Healing of the stump takes place at the cut end and the sutures which occlude the lumen of the bronchus, usually from four to six in number, must be considered as only temporary, with their main purpose to exclude the passage of air through the bronchial stump long

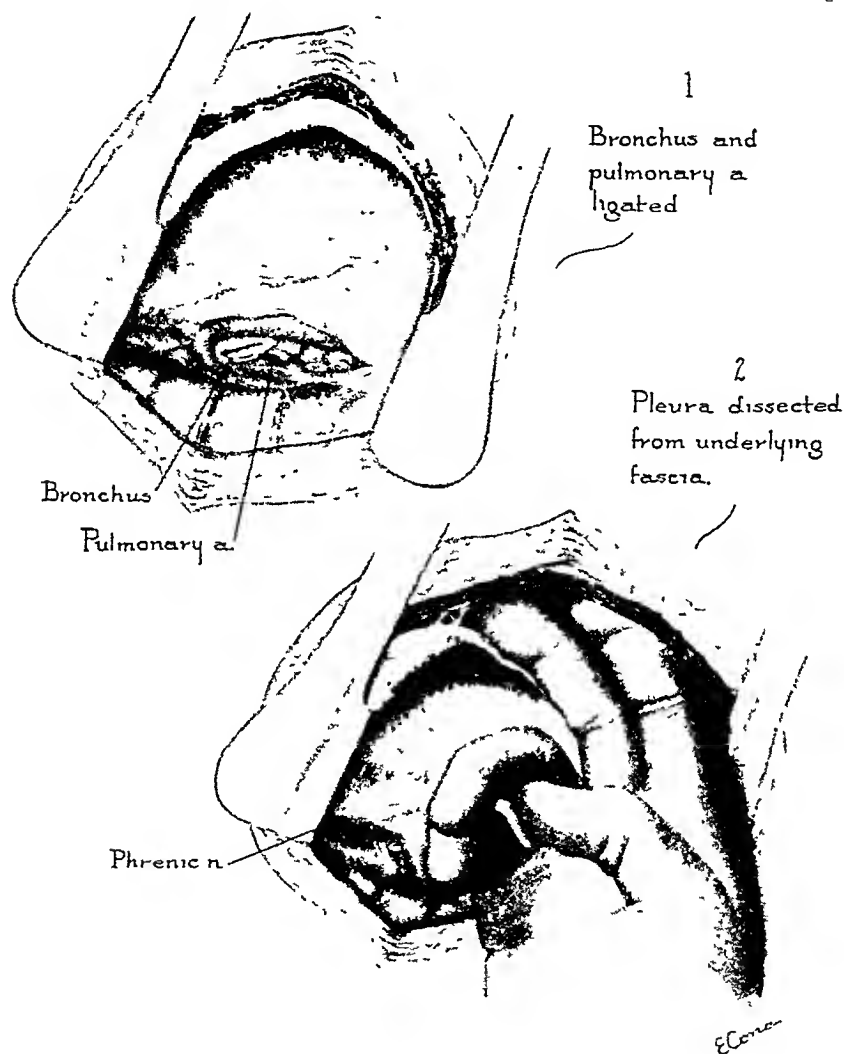


FIG. 9.—Mobilization of pleura over anterior chest wall, developing flap of parietal pleura to cover raw area of hilus. The same method can be used in mobilization of the parietal peritoneum over the vertebral gutter.

enough for the healing of the end of the bronchus to be completed, or sufficiently so, that in the event the sutures cut through, to form a tight and impenetrable occlusion of the bronchial stump that will not open up and allow air to pour into the pleural cavity. The healing of the end of the bronchial stump requires, as a rule, from one to two weeks, varying in different individuals, and seems to be completed in the majority of cases after a period of 10

to 14 days. However, there have been instances in our series in which the stump in one patient reopened after a month, one after three months and one even after eight months. However, these, fortunately, eventually healed and the patient was none the worse off except for the disagreeable experience asso-

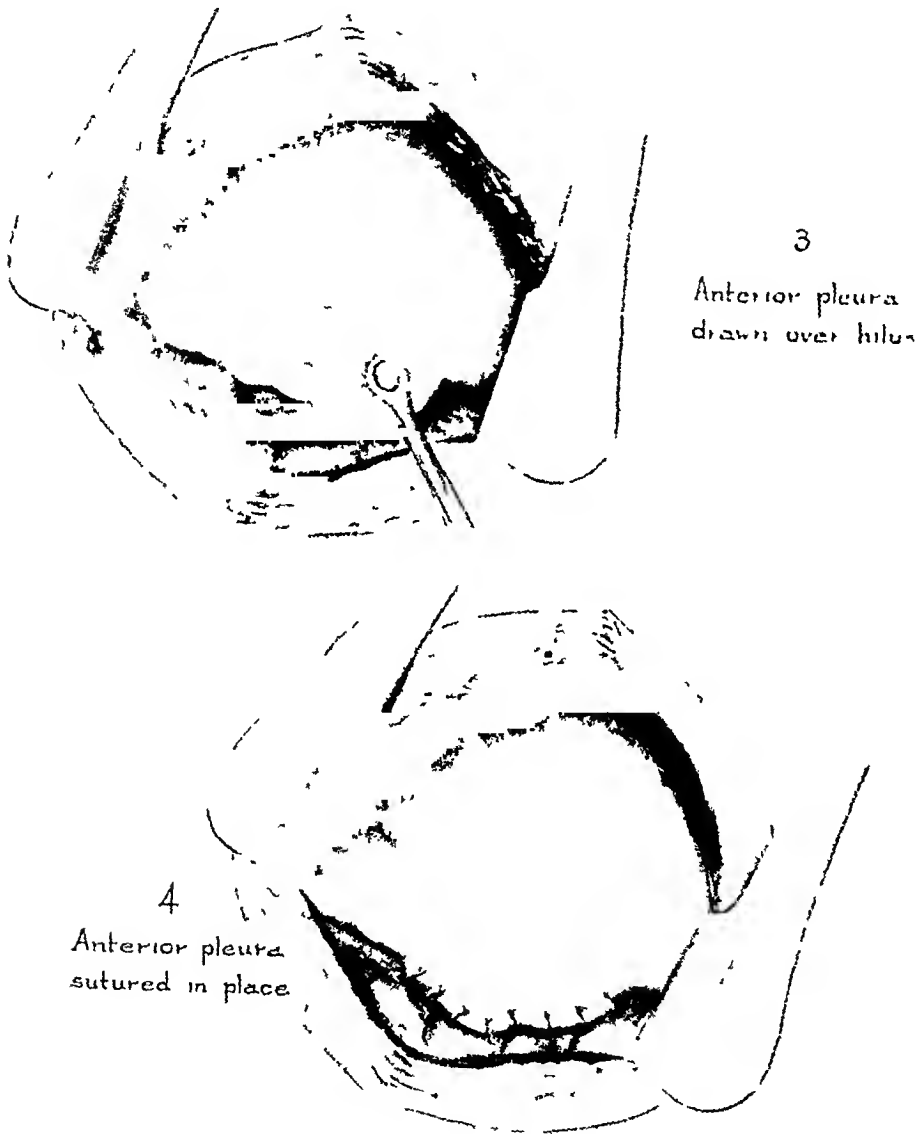


FIG. 10.—Mobilization of pleura over anterior chest wall, developing flap of parietal pleura to cover raw area of hilus. The same method can be used in mobilization of the parietal peritoneum over the vertebral gutter.

ciated with walled-off empyema, which was satisfactorily treated by drainage and irrigation with penicillin.

Interrupted mattress sutures may be employed by stitching the anterior cartilaginous wall laterally, infolding the posterior membranous portion, pro-

viding the cartilaginous rings are incised at the apex of their arc, this in the midline of the anterior surface of the bronchus. This method has been satisfactorily employed in some cases. (Fig. 7—Fig. 8.)

All types of suture material have been used—catgut, silver wire, steel wire, fascia, and others—and it is our opinion that interrupted sutures of silk or cotton would seem to be the material of choice.

Before the bronchial stump is sutured, after amputation of the lung, the inside of the remaining bronchus should be carefully inspected, for not infrequently a blood clot or even a piece of tumor tissue may be dislodged from the lung into the primary bronchus during the course of the operation. Immediately following operation the patient is again bronchoscoped while on the operating table before being returned to the ward. Often small clots and pieces of tumor tissue have been discovered not only in the bronchial stump on the operative side but even in the trachea. If these foreign bodies were not removed, aspiration into the contralateral lung might eventuate in the death of the patient.

Mobilization of the parietal pleura may be accomplished on either side by loosening the pleura from the endothoracic fascia either anteriorly or posteriorly in the vertebral gutter. No difficulty has been experienced in obtaining a sufficient amount of pleura to cover over completely and without tension the entire raw hilar area (Figs. 9 and 10).

At the end of the operation 150,000 units of penicillin have been introduced into the thoracic cavity. The intrapulmonary pressure, as the wound in the chest wall is closed, has been increased to not more than 10 mm. of mercury. The entrapped air is removed to the fullest extent possible by leaving a small catheter in the wound during closure. After the last interrupted suture is placed in the skin all the air that can be is removed by aspiration and the catheter itself is then withdrawn. No drainage of the pleural cavity is thought desirable even in the presence of infection, within the lung itself, and when purulent material has been unfortunately and accidentally spilled into the pleural cavity.

Since penicillin has been available, when gross infection has been present it has been our custom to introduce every other day 50,000 units of penicillin into the thoracic cavity. In addition, the drug is also given intramuscularly up to 50,000 units every three hours. No instances of empyema have been encountered in cases so treated, and, thus, the necessity for performing thoracoplasties to obliterate infected dead space in the thoracic cavity has been avoided.

A word of caution should be given here in regard to the possibility of the development of interstitial pulmonary emphysema as a result of increasing the intrapulmonary pressure either too rapidly or to too great an extent, in an endeavor to hyperdistend the lung on the unoperated side for the purpose of obliterating the dead space in the thoracic cavity on the operative side. Rupture of alveoli within the lung substance itself producing a mediastinal, plus extensive subcutaneous as well as visceral emphysema was encountered in one

CARCINOMA OF LUNG

case of diaphragmatic hernia followed by death from cerebral and coronary air emboli, proved at autopsy.

The final proof of the efficacy of any method of therapy naturally is a critical analysis of the immediate and remote results. Of 327 cases of primary carcinoma of the lung, as shown in Table III, 215, or 66 per cent, were inoperable, whereas, 112, or 34 per cent, were operable. This ratio of the inoperable to the operable cases is far higher than it should be, for in the majority of instances the attending physician and even the patients had been aware of a lesion in the lung for many months, and often years, before submitting themselves to operation. Undoubtedly in the future, as the field of thoracic

TABLE III
CARCINOMA OF THE LUNG
Ratio of Operable to Inoperable Cases

	No. of Cases	Percentage
Operable.....	112	34
Inoperable.....	215	66
	<hr/> 327	<hr/> 100

TABLE IV
CASES OF INOPERABLE CARCINOMA
According to Years

	No. of Cases
1934.....	2
1935.....	3
1936.....	9
1937.....	17
1938.....	22
1939.....	14
1940.....	21
1941.....	16
1942.....	22
1943.....	19
1944.....	19
1945.....	37
1946.....	14
Total.....	<hr/> 215

surgery is developed, this disproportion will be reduced. There will always be those instances in which a malignant tumor begins in the periphery of the lung, the so-called silent area, and produces no symptoms or signs until involvement of the pleural or contiguous structures renders the case inoperable. Fortunately, this group comprises only about 10 per cent of the cases of malignancy of the lung, 90 per cent occurring near the hilus, and producing warning signals early in the process of the disease. Unless for palliative reason, to rid the patient of an infected lung due to neoplastic bronchial obstruction, for example, pneumonectomy should not be performed if the tumor has involved contiguous structures. Therefore, inoperability would be manifest by involvement of the parietal pleura or any of the underlying structures.

Table IV reveals the number of cases, *i.e.*, 215, of inoperable carcinoma of the lung which have been subjected to operation from January, 1934 until July, 1946. This number does not include those patients that were clinically inoperable. The clinical findings, which we have found to indicate a spread of the tumor beyond the confines of the lung and, therefore, render the case incurable from a surgical standpoint, are the following: Metastases to the opposite lung or mediastinum, direct metastases to brain, osseous tissue, liver, skin, axillary and supraclavicular nodes, pleural effusion, clear or serosanguineous, continuous pain to shoulder or referred down the arm, Horner's syndrome, left recurrent laryngeal palsy or hemiparalysis of the diaphragm.

TABLE V
PNEUMONECTOMY FOR CARCINOMA OF THE LUNG
Operations and Mortality According to Years

	No. of Operations	No. of Deaths
1933.....	2	0
1934	1	1
1935.....	5	1
1936.....	4	2
1937.....	5	0
1938.....	7	2
1939.....	6	2
1940.....	10	0
1941.....	13	3
1942.....	9	4
1943.....	9	2
1944.....	12	2
1945.....	15	5
1946.....	14	1
	<hr/> 112	<hr/> 25

Although the number of cases of inoperable carcinoma of the lung have apparently increased since 1939, when Table IV is compared to Table V, there is very little fluctuation in the ratio of operable to inoperable cases over the same period of time. All patients with lesions of the lung which have been diagnosed probable malignant tumors should be explored regardless of the size or position of the tumor or the age of the patient. In the absence of clinical signs or symptoms of a spread of the disease from within the limits of the lung itself, the question of operability can be determined only by exploration of the chest.

In this series of cases, there have been 107 in which total pneumonectomy was performed for carcinoma of the lung.

Table V represents the number of total pneumonectomies performed each year for carcinoma of the lung, together with the deaths occurring within one month of the operation. All deaths within this time limit were considered in the group of immediate postoperative mortality because of the fact that the patients had remained in the hospital that long and although in some instances death was in no way connected with the actual operative procedure. From

CARCINOMA OF LUNG

1933 through 1939 there were 30 cases with eight deaths, or a mortality of 27 per cent. From 1940 through half of 1946, 82 patients were operated upon, with 17 deaths, or a 20.7 per cent mortality. Thus, in spite of an increase in the number of patients there was a 5 per cent decrease in immediate postoperative mortality. Undoubtedly in the future this hospital death rate will be decreased because of several reasons, such as earlier reference of cases by the general practitioners, improvements in operative technic, chemotherapy and anesthesia. In addition, postoperative care has improved remarkably. Penicillin is now given intramuscularly, by inhalations, and intrathoracically, so that the chance of developing a postoperative empyema is almost nil.

TABLE VI
PNEUMONECTOMY FOR CARCINOMA OF THE LUNG

	No. of Cases	Total	Percentage
Patients dying after various periods of time:			
Less than 1 month.....	25	25	22
1 month to 6 years			
1 month to 6 months.....	20		
6 months to 1 year.....	10		
1 year, or more.....	6		
2 years, or more.....	2		
3 years, or more.....	3		
4 years, or more.....	1		
5 years, or more.....	1		
6 years, or more.....	1	44	39
Patients living:			
1 month to 6 months.....	12		
6 months to 1 year.....	2		
1 year, or more.....	8		
2 years, or more.....	5		
3 years, or more.....	4		
5 years, or more.....	4		
6 years, or more.....	2		
9 years, or more.....	2		
10 years, or more.....	2		
11 years, or more.....	1		
13 years, or more.....	1	43	39
		112	100

Important as the immediate operative mortality is, and it should be very jealously guarded, the efficacy of the operative procedure should also be judged by the ultimate results. The duration of life following total pneumonectomy for carcinoma of the lung is shown in Table VI. It is to be noted that patients dying after various periods of time are so charted in comparison to patients still living following operation. Those dying following operation who died less than one month afterwards were considered an operative mortality. The total operative mortality of the 112 cases for total pneumonectomy for carcinoma of the lung was 22 per cent. Of the patients who are now dead, but who lived for various periods of time after operation, *i.e.*, from one month to six years, the number surviving the different periods of time was 44. This group of cases made up 39 per cent of the total. Reference must be made to the fact that of the 215 cases of inoperable carcinoma comprising this series,

the average duration of life after exploration of the thoracic cavity was five months, so that even in the group, in Table VI, which are now dead but lived various periods of time following operation, the average duration of life after removing the lung was greater by far than in those patients in which the lung could not be removed. Of the patients living at the present time, 39 per cent of the total, or 43 patients, have survived from one month to 13 years. Of this group, 12 patients have lived five years, or more; one, 13 years; one, 11; two, nine; and two, six. As they are still living there is a possibility they may live for many years. It would seem desirable to call attention to the fact that all these patients, except one who was a professional boxer, have been restored to their normal activities. They have been able to return to their former vocations and even recreations, such as golf, swimming, fishing and hunting. In all except the occasional case, since it has not been found necessary to perform a thoracoplasty, no deformity of the patient is visible from the removal of the affected organ. The remaining lung expands to fill the dead space. This intrathoracic readjustment has been reported in detail elsewhere. If these results are compared to those obtained from the surgical treatment of carcinoma of the thyroid, breast, esophagus, stomach and large and small intestine, reported over a corresponding length of time (13 years) it will be evident that removal of the lung for primary carcinoma offers at least as great if not greater probability of permanent cure as the surgical treatment of carcinoma of any other organ in the body.

Of the group of patients who lived for some time (up to six years) following operation, but who are now dead, the majority were definitely improved by relieving the coughing, hemoptysis and often extensive pulmonary suppuration with its attendant discomfort and manifestations.

CONCLUSIONS

An otherwise fatal disease, primary carcinoma of the lung, can be satisfactorily treated by surgical removal of the entire organ. Surgical measures short of total pneumonectomy are not efficacious. Postoperative mortality and longevity are at least as good as, if not better than, the postoperative results following the surgical treatment of carcinoma of other organs.

REFERENCES

- ¹ Rienhoff, William F., Jr.: Pneumonectomy: A Preliminary Report of the Operative Technic in Two Successful Cases. *Bulletin of the Johns Hopkins Hospital*, 53, No. 6, 390, 1933.
- ² Rienhoff, William F., Jr., Gannon, James, Jr., and Sherman, Irwin: Closure of the Bronchus Following Total Pneumonectomy: Experimental and Clinical Observations. *ANNALS OF SURGERY*, 116, No. 4, 1942.

1201 N. Calvert St.
Baltimore, Md.

DISCUSSION.—DR. BRIAN BLADES, Washington, D. C.: I fully agree with Doctor Ochsner and Doctor Rienhoff that the indications for exploratory thoracotomy in patients suspected of having a neoplasm of the lung, should be extended. I understood Doctor Ochsner to say that the only contraindication to exploratory operations at his Clinic was evidence of distant metastasis. This brings up the question of whether or not one should

adhere to the contraindications observed a few years ago; namely, paralysis of the diaphragm, paralysis of the vocal cord, or the presence of a pleural effusion. Should exploratory operation be recommended to a patient with any of these manifestations of extension of the tumor and, particularly, should operation be recommended if a bloody effusion is present?

Certainly these two extensive series of pneumonectomy for bronchogenic carcinoma demonstrate the great progress which has been made in this type of surgery in the past ten years.

DR. ALTON OCHSNER, New Orleans, La. (closing): I should like to reiterate the point Doctor Rienhoff made. We feel that artificial pneumothorax is extremely important as a preliminary procedure. I think it allows the cardiovascular system to adjust itself to the collapse of the pulmonary capillary bed. I should like, also, to emphasize the importance of the anterior approach. With very few exceptions we use this approach; only in suppurative disease do we use the posterolateral approach. It is so much easier to operate through the anterior approach because the distance from the chest wall to the mediastinum is less than in the posterolateral approach. Doctor Rienhoff deserves the credit for popularizing this method of approach.

In answer to Doctor Blades' question, our only contraindication to operation is evidence of distant metastasis and evidence of pleural involvement. Pleural effusion is not a contraindication, but if the fluid is bloody, or if tumor cells are found in the centrifugated specimen, the case is considered inoperable. As to paralysis of the vagus or phrenic nerve, I do not believe it is necessarily a contraindication to exploration. One patient of ours who had survived operation for three years had recurrent laryngeal paralysis. She died subsequently, but to deny that patient the benefit of exploration would be to deny her several years of life. Some of these patients have involvement of the aorta. If this is true, the lung cannot be removed, but it is surprising how many times the involvement is such that one can resect the vagus and allow the patient to go a few months or years with comparative freedom from symptoms. Our contraindication to operation is evidence of extension beyond the lung into the parietal pleura or distant metastasis—not necessarily involvement of the phrenic or vagus nerve.

DR. WILLIAM F. RIENHOFF, JR., Baltimore, Md. (closing): Dr. Brian B. Blades asked whether one is ever justified in performing a lobectomy for carcinoma of the lung. Theoretically, and under quite unusual circumstances, I imagine this procedure would be warranted. I have known of only one case, operated upon by Dr. Edward Churchill, in which apparently a complete cure was obtained following lobectomy. Two brothers working under similar conditions developed malignant growths in the lung at about the same time. One succumbed because the growth was inoperable and the other was alive and well several years later following lobectomy. It is my opinion, however, that this case is the exception that proves the rule. I have been raised in the school of surgery in which eradication of the entire organ affected with carcinoma has been and is considered the proper surgical approach to this problem.

I agree with Dr. Alton Ochsner that the field of operability for carcinoma of the lung should be, and actually is being, extended. It just so happens that in those patients in whom a recurrent laryngeal palsy on the left side existed the tumor turned out to be inoperable. I think Dr. Evarts Graham successfully operated upon a patient in whom such a palsy existed prior to operation.

Dr. Alfred Blalock suggested that I mention briefly four patients that have been operated upon for solitary metastases. Two cases operated upon by me were instances of solitary metastases of a slow-growing fibrosarcoma originating in the tendon sheath of the thigh. Doctor Blalock successfully operated upon two patients in whom there were simple metastases from the colon. It is impossible to say how long these patients will live, but I am inclined to think that in the absence of metastases other than in one lung, one is perfectly justified in performing a total pneumonectomy.

A CONCEPT OF TOXIC GOITER*

WILLARD BARTLETT, M.D., D.Sc.

ST. LOUIS, MO.

THYROTOXICOSIS is a constitutional malady of which we have incomplete knowledge obscured somewhat by therapeutic developments of the past quarter of a century. The ultimate outcome of its two forms, the adenomatous and the diffuse hyperplastic, may be essentially different, but it is well to consider them together, with frequent allusions to the features in which they differ.

Those of us who were operating upon toxic patients in the early 1900's realized that they gradually got ready for successful surgery, most of them, with treatment, without treatment, or in spite of treatment previous to Plummer's introduction of Lugol's solution in 1922, which very definitely shortened the preoperative period, which was still further shortened some 20 years later by the advent of the "thio-uro" group (potentially dangerous drugs).

Henry Plummer, of the Mayo Clinic, was the first to outline the *average* characteristic course of the disease as result of his analysis of 5,000 untreated patients. He demonstrated that the malady pursued a *cyclic* course, each cycle running about 15 months, of which the first half (7.5 months) showed decline in health, while the second half evinced spontaneous improvement. The patient sank to a lower level during each succeeding cycle, about ten of them being required to "*burn her out*." There are, of course, exceptions to all rules and I have seen two glaring ones of Doctor Plummer's. One young woman died in crisis within one week of her first thyrotoxic symptoms; another older woman experienced a free interval of 13 years between her first and second toxic episodes, then died in crisis during this last one.

An experienced goiter surgeon is frequently called in consultation over a patient dying in crisis, a situation which has, in my own experience, been precipitated invariably by one of two mental attitudes; namely, (a) impatience on the patient's part; or (b) ignorance on the surgeon's part that such a patient, treated or untreated, tends in most instances to become a safe operative risk if only he waits long enough.

The subject may well be considered under four heads:

1. Nature of the maladies.
2. Preoperative care of the patients.
3. Criteria of operability.
4. During and after operation.

The nature of the two maladies is similar in so many particulars that they may be considered together, insofar as six salient features are concerned; *viz.*,

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

(1) Edemas are characteristic of both of them when they are at all advanced, due in great part, no doubt, to heart involvement at a period when no definite cardiac lesion can be made out. In diffuse hyperplasia the heart manifestations are likely to prove functional in character and to be promptly and completely relieved by thyroidectomy, while the toxic adenoma may produce *anatomic* lesions which tend to persist even after the goiter which produced them has been removed.

(2) Hypoproteinemia is practically characteristic of both forms of toxic goiter, hence, furnishes one of our leading motives in the preoperative care of every toxic patient. The objective here can usually be met by a sufficiently prolonged feeding of 115 Gm. (calculated) daily of the albuminous foods given to the ordinary hospital patient.

(3) Radiation of body heat is affected in all of these patients. One of the most common and most bitter of their complaints is occasioned by the circumstance that they can not get rid of it at a normal rate. We have been greatly aided in the preparation of such patients for operation by resting them on a veranda (weather permitting) placing them upon a canvas cot instead of a mattress, then using a fan most carefully.

(4) Anoxemia on Exertion.—This manifestation is usually of extreme degree in patients who present the other well-known features of the malady, especially in the diffuse hyperplastic form. The well-known Army "hopping up and down" exercises will readily elicit this symptom if present in any noticeable degree.

(5) Prothrombin deficiency may be present without having made itself apparent until practically uncontrollable bleeding becomes apparent at operation, hence, preparation for transfusion should be a part of the operating room set-up whenever this possibility can not be ruled out, since far too much blood may be lost, although careful hemostasis is practiced as far as recognizable sources of hemorrhage are concerned.

(6) Liver function is undoubtedly impaired in every pronounced case of thyrotoxicosis; it is well, therefore, to carry out some of the well-known liver-tolerance tests in every one of these patients who exhibits a marked case of the disease in either of its two forms. Liver-death is probably more common than usually supposed, hence, is not to be taken lightly as a possibility.

The *preoperative* care of these people may spell the difference between success and failure in the treatment of them. It has been recognized by men who study them that very few enter the hospital in a condition that warrants immediate operation, something which is possible for many patients who are afflicted in other ways. We are able to prepare the diffuse hyperplastic (exophthalmic) patients more quickly and more adequately than the adenomatous ones, since we possess at least two specific remedies for them, while for the last named we are restricted to the general measures which usually benefit both varieties; namely, (1) diet, stressing proteins, at least 115 Gm. daily; (2) rest, apportioned to individual needs; and (3) sedatives in excess of any ordinary need.

We have used iodides in both forms of the disease since Plummer introduced the idea in 1922, though many students of the malady feel that it is not effective in the adenomata. Their value seems to be apparent in the first weeks of their use, which means, usually, that they should be employed only as a preliminary to an operation which has been decided upon. The full effect of iodides can not be secured a second time, and they are surely not indicated for the treatment of a chronic case.

Thiouracil, and similar compounds, are the recent and most effective additions to the list of medicaments which profoundly influence hyperplastic goiter, though they are not equally valuable in the treatment of the adenomata. We have employed them with truly astonishing results, and have been fortunate enough to escape any of the complications or fatalities observed by others, though blood, urine, *etc.*, have been scrutinized at frequent intervals by a capable internist and pathologist at De Paul Hospital. Still, we realize that agranulocytosis, severe anemias and even fatalities have followed their use, and that it is really a question of time until misfortune overtakes any one who employs this useful, though potentially deadly, compound which certainly should be withdrawn at the appearance of trouble.

Thiouracil had not been long in use before operators noted that patients prepared with it bled to a totally unexpected degree; in fact, they seemed to "weep" blood from sources too small for identification. This embarrassing tendency was corrected shortly thereafter by withholding the drug one week previous to operation, then changing to iodine, or to an iodide, with the happy result that no more than the expected amount of bleeding occurred. We have not limited the use of thiouracil to the treatment of diffuse hyperplastic goiter alone, knowing that hyperplasia occurs in thyroid tissue between the nodules of an adenomatous goiter as well as within the adenomata themselves. We have often been gratified by using it thus, though we must admit that its field of greatest usefulness is in the preoperative treatment of the diffuse hyperplastic form of toxic goiter.

We feel that our own *criteria of operability* deserve all the credit during the lengthy periods in which our operative results have been wholly satisfactory. There has been a calamity, sometimes a fatality, every time we have digressed from one or more of them. They are six in number, a certain amount of originality being claimed for the sixth: (1) circulatory; (2) nutritional; (3) central nervous; (4) excretory; (5) metabolic; and (6) breath-holding (voluntary apnea).

The choice of a toxic patient for operation is frequently rendered difficult as far as the heart is concerned by a coincidental *anatomic* lesion of the circulatory system which has no connection with the goiter, toxic or otherwise. After an accurate estimate of the true state of affairs, a prognosis based upon it will do much toward avoidance of the disappointment sure to arise when promised heart improvement fails to follow removal of the goiter which the patient has been told was responsible for all her symptoms. It may occasionally be good judgment to remove half the load by thyroidectomy in many such

instances, but the patient must be told that chronic vascular trouble remains. *Decompensation* always precludes operation until the patient has had the cardiac mechanism restored; this does not take long in hyperplasia, as a rule, while it may be a very lengthy procedure in toxic adenoma. An old assistant of mine once said of such patients: "Let them do their own dying," a solution which is surely more acceptable than the death which follows operation upon a patient who is not ready for it.

We have seen a few patients who have required a year of treatment before successful operation became possible, while, on the other hand, consultation over a patient dying after thyroidectomy has usually elicited this explanation to me: "We operated because the patient had stopped improving." Such operators are usually men of limited *thyroid* experience. We often have a capable cardiologist examine the patient before selecting a date for operation, though sufficient circulatory improvement should be apparent to any well-trained internist or to a capable surgeon himself. But *remember at all times that the circulatory criteria are the most important of them all.*

Nutritional changes come second on our list. The patient who has lost much weight rather suddenly is never a good risk. Willard Bartlett, Jr. has made the very pertinent observation that loss of weight is not infrequently preceded by a sudden, short, sharp gain, something we have noted too often for it to be mere coincidence, though it seems not to have been widely commented upon.

Central nervous manifestations are surely important criteria, particularly the more severe forms of them. We long ago learned by bitter experience that an insane patient, also one recently so affected (diffuse hyperplasia), invariably dies soon after thyroidectomy.

Excretory phenomena are to be taken seriously, particularly diarrhea and vomiting. We never plan an operation in such cases until at least 50 per cent of the lost weight has been regained, provided, of course, that the other five criteria are satisfactory.

Basal metabolism figures are important only when a comparative study of several observations can be made under similar circumstances, preferably in the hospital under truly *basal* conditions.

Voluntary apnea (our breath-holding test) would seem to be the most convincing of all six criteria, particularly since, to some extent it embraces features of the other five which have preceded it. I first proposed the test at the Dallas meeting of the American Medical Association in 1926, after noting that several patients, thought to be ready for operation, had to be hurriedly returned to bed because they became cyanotic when an inhalation anesthetic was started. Clinical experimentation soon proved that such *unprepared* patients could be identified during breathholding before a *needless* trip to the operating room. The technic of the test, as now used, and its full value, were not realized until Willard Bartlett, Jr., after studying it further, published his article: "Duration of Voluntary Apnea in Thyrotoxicosis: An Index of Stability and Criterion for Operability," Surg. Gynec. and Obst., 63, 576-582, 1936. Two phases of

this problem are now recognized; namely, the importance of the relationship between (1) breath held after inspiration; and (2) breath held after expiration. It is normally held about half as long with an empty chest as it is with chest filled; any great alteration in this 2:1 ratio shows that the patient is *not* prepared for operation, while the same conclusion may be drawn if the breath is not held 40 to 50 seconds after deep inspiration. It may be noted that normal persons hold the breath with full chest from 60 to 100 seconds, while trained athletes extend this to three minutes at times, and there are said to be instances on record of men being saved from drowning after complete submersion for full 15 minutes. A knowledge of the patient's background is, therefore, essential to an adequate interpretation of this test in the individual case.

During and after operation decidedly weighty conclusions must be arrived at and vitally important measures carried out.

The method of anesthetising the patient demands our first attention. Toxic patients should not get enough of a general anesthetic to make them bleed excessively while, on the other hand, the nervous system is unduly sensitive, hence, must be protected to a very definite degree. This we accomplish by the use of a combined nerve block and inhalation. (The method was described in detail in "A Safe and Satisfactory Method of Anesthesia for Toxic Goiter Patients," Willard Bartlett and Willard Bartlett, Jr., Surg., Gynec. and Obstet., 58, 737-740, 1934.)

Our idea is to create skin and fat analgesia by blocking the superficial cervical plexus at the posterior border of the sternomastoid, as had been done by so many others, but to this we add a block of the descending branch of the hypoglossal, thus, securing a like effect on the fasciae and muscles all the way down to the gland itself, which is rendered insensitive by blocking the nerves entering the two upper poles *after* they have been exposed. The entire thyroid region is, thus, rendered devoid of all sensation for an hour or more. All needle pricks, tractive or retractive discomfort are "covered" by a minimum of ethylene gas. This method, which seems to have been widely adopted, is so successful that we frequently employ it on *nontoxic* patients, omitting the use of a general anesthetic entirely.

A second therapeutic measure carried out by us *during operation* is the intravenous introduction of 200 cc. of 25 per cent hypertonic dextrose, based on the observation that patients who die from goiter operation present the picture of cerebral edema, which, quite naturally, suggests the desirability of the hypertonic treatment.

Our third suggestion for the period of the operation, always a vital time, has to do with the excessive *use of oxygen*, whether or not it seems particularly indicated; this seems to come as a matter of course in view of the anoxia on exertion which these patients all show when first seen.

A fourth consideration has to do with *sodium iodide*, one or two ampoules of which are added to the intravenous injection at the table. This is particu-

larly valuable for the patient who has been prepared by administration of thiouracil, and who tends to bleed without an iodide.

In the fifth place, we add a large dose of *vitamin-K* to the already mentioned intravenous iodide, though three daily administrations of it have been carried out previously during the late preparatory period.

We realize the need of fluid for all patients, hence, the *hypodermic* introduction of 2,000 cc. of 5 per cent dextrose is started after the patient is returned to bed, but so slowly absorbed as not to destroy the effect of the *hypertonic* solution which has preceded it.

Another consideration has to do with the extreme protein need of the toxic goiter patient. We tried to meet this need by feeding during the pre-operative period, so it seems logical now, during the period of extreme stress, to inject under the skin one or two ampoules of *amino-acids* (Stearns), meeting in this way any added acute load.

Immediately following the operation we give *sedatives*, enough to insure perfect quiet on the patient's part, though less than the expected degree of pain follows a well-carried-out nerve block.

When temperature rises to 102°F. in the early postoperative course we have four ice-bags applied, one to the forehead, one to the precordial region, and one to the inner aspect of each thigh. The patient is closely watched and the bags quickly removed if the body temperature is forced to a subnormal degree.

Fluid intake, by whatever route, is strictly limited, as has been mentioned, during the first few hours while cerebral and other edemas are considered possible.

Propyl thiouracil would seem to be *comparatively* harmless, and we have proved by their use in thousands of cases, that the six criteria of operability we are presenting, cover all essential risks, hence, this combination should reduce the mortality of thyroidectomy to almost the vanishing point. This is a prediction in which we may well take pride when it is remembered in comparison that Dr. C. H. Mayo, the incomparable pioneer in the field of toxic goiter a half century ago, experienced a mortality of 25 per cent in his first short series of the then little understood toxic patients, as he told me in January, 1902, when I first visited him and his equally promising brother who were both then new to fame.

607 N. Grand Ave.
St. Louis 3, Mo.

THE USE OF THIOURACIL, THIOBARBITAL AND PROPYL THIOURACIL IN PATIENTS WITH HYPERTHYROIDISM*

FRANK H. LAHEY, M.D.,

DEPARTMENT OF SURGERY,

AND

ELMER C. BARTELS, M.D.,

DEPARTMENT OF INTERNAL MEDICINE,

THE LAHEY CLINIC,

BOSTON, MASSACHUSETTS

THE USE OF AGENTS capable of bringing to normal the elevated basal metabolic rate of hyperthyroidism has greatly reduced the complications of this abnormal metabolic state. Astwood, to whom we are all indebted for his work on these drugs, has proposed three different drugs of the thiourea group for employment in this disease, first thiouracil, then thiobarbital and now propyl thiouracil.

As is the case with all new agents, particularly while they are in the trial stage and experience with them is being gained, many premature, over-optimistic and conflicting statements are made about them. It is for this reason we think that it is important for anyone who has had a large experience with them to keep reporting their results for others while they are gaining their own experience with these agents. These drugs are extremely powerful and effective and because of this powerful effect on inhibiting the synthesis of thyroxin they have in certain cases an equally powerful capacity to depress bone marrow function and produce agranulocytosis which can and already have brought about a considerable number of avoidable fatalities. We have used one or more of these agents over a period of three and one-half years and have now prepared 660 patients with various types of hyperthyroidism for thyroidectomy, and in addition have employed these agents in a series of 21 cases over a long period of time to determine whether they can be used as a substitute for operation. We would like to propose a series of pertinent questions concerning these drugs and attempt to answer them from our experience which is now large enough and long enough to permit answers with a reasonable assurance of their soundness.

HOW DO THESE DRUGS ACT TO REDUCE THE BASAL METABOLIC RATE?

In attempting to answer this question, one is able to state only the results obtained by the use of these drugs. We know that if given in an adequate dose they completely halt the synthesis of inorganic iodine into diiodotyrosine on into thyroxin, as is proven by the drop in the protein-bound iodine. The basal metabolic rate drops and if the agent is continued long enough, myxedema results and is maintained as long as the drug is given.

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

Unlike iodine which produces prompt and striking histologic change in the thyroid gland, which at least is relatively proportionate to the change in the clinical and metabolic picture, these three agents, thiouracil, thiobarbital and propyl thiouracil, produce even more striking effects upon the clinical and metabolic picture but with practically no change in the histologic picture. Since it is true that the function of the thyroid cell by which iodine is synthesized into thyroxin is not demonstrable by histologic examination, so the method by which thiourea agents stop the synthesis of thyroxin is as yet not satisfactorily explained. It is important to have in mind, as relates to the question of whether or not these drugs will prove to be a complete or partial substitute for subtotal thyroidectomy, that the pathologic histology (hyperplasia) which originally brings about hyperthyroidism is still present even after these drugs have reduced the basal metabolic rate to normal, and that on stopping these agents the necessary factor for the restoration of an elevated metabolism (hyperplasia) is still present.

WILL THESE AGENTS ALWAYS BRING THE METABOLISM TO NORMAL?

Since many patients become iodine-fast or iodine-resistant, the question has often been asked as to whether or not this condition arises in patients with hyperthyroidism while being treated with these drugs, thiouracil, thiobarbital or propyl thiouracil. In spite of the fact that we have been told by others

TABLE I

COMPARATIVE DAILY DOSAGE OF ANTITHYROID DRUGS

Drug	Daily Dosage, Mg.
Thiouracil	600
Thiobarbital.....	50
Propyl thiouracil	200

that this occurs, it has not been our experience. There has been no patient in whom, if given one of these drugs in a large enough dose over a long enough period of time, if not compelled to stop it because of a complication, we have not been able to bring the metabolic rate to normal.

To discuss dosage first and length of time the drug needs to be administered afterward (Table I), we believe that the drugs thiouracil and thiobarbital which have been employed over the longest period of time have had their effective doses well established—thiouracil 0.6 Gm. and thiobarbital 50 mg. daily. The drug which we now employ to the exclusion of the other two, propyl thiouracil, coming as it has after the other two, has only recently had its dosage in comparable effectiveness established. The factor of inadequate dosage was early responsible for the poor response of some of our patients, and because of the inadequate doses administered, may be responsible for the assumption that there are no complications from the use of propyl thiouracil. The dose which was originally suggested, 75 to 125 mg. daily, in preparing patients with hyperthyroidism for surgery was entirely inadequate

to prepare these patients and when they came to surgery they were not entirely free from hyperthyroidism. It was not until the dosage was increased to 200 to 225 mg. daily that full control of hyperthyroidism was accomplished.

Since most of the patients to whom we administer these metabolism-depressing agents are receiving it in preparation for thyroidectomy, it is important to be able to estimate with reasonable accuracy when their metabolic rate will reach normal and when they will be ready for operation. With the shortage of hospital beds and since many of these patients live at a considerable distance from the clinic, we must be able with reasonable sureness to predict when the patient is to return to the hospital, free from toxic symptoms and with a normal or practically normal basal metabolic rate, for subtotal thyroidectomy.

This prediction is based upon what are now some quite soundly established facts. When a patient is upon an adequate dose of thiouracil, thio-barbital or propyl thiouracil, thyroxin will no longer be manufactured, and although these drugs will abolish the synthesis of thyroxin, they have no effect whatever upon the thyroxin which is already synthesized and stored. From this it can be seen that the time required to bring the elevated metabolic rate to normal depends upon the amount of already synthesized thyroxin in storage.

The time required to bring the elevated basal metabolic rate to normal, in our experience, is determined from the following factors: the type of thyroid disease—primary hyperthyroidism or adenomatous goiter; the duration of the disease and whether or not iodine had been taken previously. Patients with primary hyperthyroidism who have had the disease nine months, or less, and have not taken iodine have a daily drop of 1.3 in the basal metabolic rate; if iodine had previously been taken, the drop is 1 per day. If the hyperthyroidism is over one year in duration, irrespective of iodine, the drop is 1 per day.

Patients with toxic adenomatous goiters, particularly those who have been treated with iodine before preoperative preparation, require a much longer period of time to restore the basal metabolic rate to normal because these glands, with their large store of thyroxin-laden colloid, have greater reserves of thyroxin. In this type there will be a drop in the metabolic rate of approximately 0.5 per day. The longest time we have given these agents to bring the basal metabolism to normal was 180 days in a patient with a large, toxic adenomatous goiter who had been receiving iodine for a long period of time before preparation for surgery. Treatment to be satisfactory must be individualized.

WHICH OF THE THREE DRUGS, THIOURACIL, THIOBARBITAL OR PROPYL THIOURACIL, IS THE MOST SATISFACTORY AND WHY?

Now that an adequate dose of propyl thiouracil has been established, it can be said that all three of these agents are equally effective in lowering the basal metabolic rate. Each reduces the metabolism as positively and with

equal promptness, so the choice of agent must be made solely on the basis of the percentage of complications associated with each agent and the percentage of cases in which it is necessary to abandon the administration of the drug (Table II). Of the three agents, thiobarbital is the most dangerous, having an incidence of complications of 28 per cent. Thiouracil is next in risk of complications, the incidence being 9 per cent, and propyl thiouracil is by far the safest, 2 per cent.

Because of the equal effectiveness and low incidence of complications with propyl thiouracil, we believe that, with one exception, the use of thiouracil and thiobarbital, with their high incidence of complications, should be abandoned and all patients treated with propyl thiouracil. The one exception to

TABLE II
 INCIDENCE OF REACTIONS TO ANTITHYROID DRUGS
 (Operated Cases)

Drug	Patients Treated, Number	Reactions, Number	Per Cent
Thiouracil	381	34	9
Thiobarbital	28	8	28
Propyl thiouracil	260	6	2
Total.....	660*		

* Nine patients received both thiouracil and thiobarbital.

TABLE III
 TYPES OF REACTION TO ANTITHYROID DRUGS

Thiouracil	Thiobarbital	Propyl thiouracil
White blood cell depression	White blood cell depression	White blood cell depression
Fever	Fever	Fever
Skin rash		
Swollen salivary glands		
Edema of skin		
One death—agranulocytosis	No deaths	No deaths

this statement is the occasional case under treatment with propyl thiouracil in which a complication arises; one may substitute thiouracil for propyl thiouracil and finish the preparation without further complications. Thiobarbital, with its high percentage of serious complications, more than one in four, should be abandoned.

WHAT ARE THE COMPLICATIONS, HOW ARE THEY TREATED, AND
 WHEN IS THE DRUG TO BE STOPPED?

The complications (Table III) associated with the use of these drugs are, in our experience, largely associated with the first two drugs, thiouracil and thiobarbital, and are depression of the white blood cells, skin eruption, fever reactions (associated with the generalized symptoms of joint pains and

backache), and salivary gland enlargement. One case of pancreatic enlargement has been reported which produced severe pain and a palpable tumor which required operation. With the known capacity for these drugs to produce pancreatic hyperplasia it is well to have in mind that such a complication might occur.

In our experience with propyl thiouracil in preparing 260 patients for surgery there have been but two types of complications, and those in limited numbers; one patient had fever and five patients showed depression of the white blood cells. In four of these five patients the depression was mild and in one it was severe, with agranulocytosis, demonstrating the relative safety and desirability of this drug as compared with thiouracil and thiobarbital.

Since the fatalities which have occurred during the administration of these drugs have been solely in those patients having bone marrow depression (leukopenia and neutropenia), two questions naturally arise and require answers: how often should white and differential counts be made and at what lowered levels of total and differential white counts is it desirable to omit treatment with these drugs? Also, what are the causes of the fatalities in the patients with agranulocytosis produced by these drugs and what treatment is advisable? If reports of the white and differential counts were available every day, one would have safe control of these patients, but this is impossible and hardly necessary; a count every 10 to 14 days is all that seems necessary. When the white blood count falls as low as 4,500 and when the granulocytes are found to be reduced to 45 per cent, further administration of these agents should be discontinued or carefully scrutinized.

Fatalities in the group of patients with low leukocyte and granulocyte counts are the result of the occurrence of infections of a severe character and serious nature at a time when the depressed bone marrow is unable to produce an adequate number of granulocytes with which to deal effectively with the infections. As a result of having dealt with a number of these agranulocytic states, in which early in our experience one fatality occurred, we have learned that penicillin is the sole agent upon which one can place dependence, acting as it does to control the infection, while by omission of the drug, thiouracil thiobarbital or propyl thiouracil, the bone marrow is permitted to regain its function. Because of this we urgently stress to patients the necessity of reporting promptly the development of sore throat or any other type of infection. We have seen no benefit from the use of vitamin B₆ (pyridoxine) or the use of liver extract in patients with agranulocytic states resulting from one of these three drugs. At the earliest possible discovery of an agranulocytic state, the omission of the drug is essential, with the prompt employment of large doses of penicillin intramuscularly and by throat spray.

SURGICAL DISADVANTAGES OF THE THIOUREA GROUP OF DRUGS

Since this group of drugs, while lowering the basal metabolic rate to normal, still leaves the thyroid gland in a state of hyperplasia, it is obvious that, as was the complaint of every surgeon who operated upon hyperthyroid

patients prepared solely with one of these drugs in the presence of such hyperplasia, operating conditions would be unfavorable, which is distinctly an understatement of fact—they were, in fact, almost impossible. Until we had learned how to bring about involution of these hyperplastic glands with iodine we know of no operation which was more technically distressing than that of subtotal thyroidectomy in a patient with primary hyperthyroidism whose basal metabolic rate had been brought to normal. All the advantages of operating upon a patient freed from his toxicity were more than offset by the technical difficulties encountered—friability of the gland, uncontrollable bleeding and inability to obtain satisfactory anatomic exposure. By the plan of omitting the thiouracil or propyl thiouracil for the last week of treatment and administering iodine for the last three weeks of treatment, these disadvantages are completely overcome.

Except in those patients with dangerous states of thyroid toxicity (crisis) or with dangerous complications (cardiac failure) an estimate is made on the basis of the data already discussed of the period of time necessary to administer propyl thiouracil in order to bring the basal metabolic rate to normal. This period is divided into weeks and the patient given propyl thiouracil, 100 mg. every 12 hours, up to the last week, during which week the drug is omitted. It is omitted for the last week because its effect will be maintained for that period of time and, more important, we have seen agranulocytic effects appear up to a week after the withdrawal of the drug, and we wish to avoid even the remote chance of such an occurrence at the time the patient is ready for operation or immediately after the surgical procedure. We had thought it undesirable to combine the administration of these thiourea drugs with the simultaneous administration of iodine because it was feared that iodine would lessen their metabolism-lowering effectiveness and prolong the period of time necessary to bring the metabolism to normal. The latter assumption has not proved to be true, as shown by recent experiences, and now the plan of therapy has undergone modification in that, in addition to the two groups of cases already cited, patients in thyroid crises and patients with severe hyperthyroidism and heart failure, all patients with primary hyperthyroidism now receive propyl thiouracil and iodine simultaneously. The addition of iodine has prolonged the response to therapy of the group who had a 1.3 drop in the basal metabolic rate, now, the response of all patients with primary hyperthyroidism is a drop of 1 in the basal metabolic rate a day. This modification was brought about by the fact that we have seen patients, especially those in dangerous states of hyperthyroidism, get worse during their first week of treatment when on thiouracil or propyl thiouracil alone. Although we know the metabolism-lowering effect of iodine upon the thyroid is ultimately less positive and dramatic, its immediate effect is more prompt. The two drugs are now given from the first day of treatment and continued in combination throughout the entire period of preparing these patients for operation. It should be mentioned that patients with adenomatous goiters do not require iodine therapy.

HOW LOW SHOULD THE METABOLISM BE REDUCED?

While it is not of great importance, it is of value to call attention to the fact that occasionally patients who have been prepared for surgery over a considerable period of time with these drugs may report for operation with low metabolic rates and in varying degrees of myxedema. Two features of this state and their relationship to possible postoperative difficulties are worth keeping in mind; one is that every patient upon whom a subtotal thyroidectomy is done will have varying degrees of postoperative edema of the larynx which, if superimposed upon some myxedematous infiltration of the larynx and cords which occurs in patients with marked hypothyroid states, will result in difficulty with breathing owing to a temporarily inadequate airway. It is also well to call attention to the fact that patients in these hypothyroid states are particularly sensitive to morphine, causing a depression of the respiratory rate, and that the combination of these two undesirable states can and has made it necessary for us in one case to perform a tracheotomy; had we operated upon this patient in a normal instead of a minus metabolic state, a tracheotomy would have been avoided.

WHICH PATIENTS SHOULD BE TREATED PREOPERATIVELY WITH THESE DRUGS?

Our early preoperative use of these drugs was limited to patients having severe hyperthyroidism (35 per cent of the total hyperthyroid patients), many of whom had complicating diseases. More recently, because of the lessened incidence of reactions to propyl thiouracil, an increasing number of patients are now receiving this type of preoperative therapy, and in the future perhaps most patients will be so treated. We realize, however, that Lugol's solution alone is very effective as a preoperative measure in patients with mild primary hyperthyroidism. A high percentage of patients with adenomatous goiters has from the onset been prepared with these drugs since patients with this type of hyperthyroidism make up a large percentage of the increased risk cases and little or no benefit is to be expected in these cases from the administration of Lugol's solution. As many patients must now wait for weeks before a hospital bed is procured, it seems wise to give treatment even to the less toxic patients so that on their admission to the hospital for thyroidectomy the hyperthyroidism is fully controlled and risk of thyroidectomy abolished.

Patients with severe, complicated hyperthyroidism are bound to benefit most from therapy since, irrespective of the type of complication, these patients can now be restored to a no-risk status. There were 115 thyrocardiacs among the 660 patients treated. Before the use of these new drugs, thyroidectomy was undertaken in thyrocardiac patients with great risk, the operative mortality being 6.7 per cent. There was but one death (the only one in the 660 patients—see Table IV) on the second postoperative day as a result of coronary disease. This patient appeared well but died suddenly after having recovered from the immediate effects of the operation. This one death evi-

HYPERTHYROIDISM

dences a great saving in life when compared with the estimated mortality in the past of eight deaths in a similar group of thyrocardiacs.

Eight patients were in the various trimesters of pregnancy and in these patients preoperative treatment was carried out in the usual way without concern for the pregnancy. All had thyroidectomy without incident and the pregnancy proceeded normally with each patient delivering a normal baby.

There were ten children under the age of 15, all with severe primary hyperthyroidism, who received treatment, giving full doses of the antithyroid drug (200 mg.), identical to the dosage employed in the older patients. The response to treatment followed the usual predictable pattern until there was full control of hyperthyroidism, at which time subtotal thyroidectomy was undertaken, without reaction.

TABLE IV
OPERATIVE MORTALITY—THYROIDECTOMY
(Preoperative Antithyroid Treatment)

Total number of patients.....	660
Postoperative deaths (2nd day postoperatively, coronary infarct).....	1
Percentage mortality.....	0.15%

There were four patients with psychoses (either primary or secondary to hyperthyroidism) who received treatment with striking ease and great benefit. These patients had mental conditions which would seem to contraindicate thyroidectomy, but improvement was sufficient in all cases to permit thyroidectomy under ideal conditions.

The 26 patients who had associated diabetes were also aided by this treatment. In some the diabetes became latent and, of those requiring insulin, the amount of insulin was reduced and the glycosuria was less difficult to control before and immediately after thyroidectomy.

The use of thiouracil, thiobarbital and propyl thiouracil has permitted a change in the approach to the treatment of diseases complicating hyperthyroidism. Before the era of these drugs the policy was to treat the hyperthyroid condition first and then the complicating disease. Now the hyperthyroidism is placed under control and then, if necessary, the complicating disease is treated, followed by thyroidectomy. One patient with frequent, recurring gallstone colic and one patient with thrombocytopenia were treated in this way. The latter case would have represented a serious problem since splenectomy, without control of the hyperthyroidism, would have been done with great risk and the danger of doing a thyroidectomy in the presence of extremely low platelets would have been equally great.

WILL THESE DRUGS BE A SUBSTITUTE FOR THYROIDECTOMY?

As already mentioned, the microscopic studies of the thyroid tissue removed at operation in patients receiving these drugs without the simultaneous use of iodine did not reveal regressive changes but there was a tendency toward increased hyperplasia of the thyroid gland. It was, therefore, con-

cluded that since the thyroid gland remained hyperplastic and, as observed clinically, the thyroid did not decrease in size, permanent cure of hyperthyroidism is not to be expected from the administration of these agents. We have had prolonged experience with 21 patients with primary hyperthyroidism who received thiouracil, until the hyperthyroidism was controlled, and observations were continued after withdrawal of the agent to determine their clinical course. All the patients had primary hyperthyroidism; 11 had recurrent primary hyperthyroidism. Treatment with thiouracil was begun in all patients with a dose of 0.6 Gm. daily; in some it was continued at this dosage up to the time of its withdrawal and in others the dose was gradually decreased as improvement was noted. Thiouracil was administered for as long as 20 months in one case. The shortest period of treatment was two months. After the withdrawal of the drug, eight patients have remained in remission and 13 patients have suffered a relapse of hyperthyroidism.

An analysis of the two groups of patients, those with relapse and those remaining in remission, revealed that the duration of administration of thiouracil after restoration of the basal metabolic rate to normal was not a factor in determining the duration of remission that followed since prolonged remissions occurred after short therapy and prompt relapse was observed after prolonged treatment. The eight patients still in remission had mild hyperthyroidism, with only slight enlargement of the thyroid gland, or small recurrent remnants. Those who had relapses had moderate to severe hyperthyroidism with large thyroid glands or large recurrent remnants. These observations indicate that thiouracil or its allied drugs have little to offer from a curative standpoint in cases of severe hyperthyroidism but that in mild hyperthyroidism with slight thyroid enlargement they may cause a remission similar to that which has been observed following the administration of Lugol's solution, or remissions which at times occur spontaneously. Since the basic etiologic factor which causes hyperthyroidism is still undetermined and as thiouracil probably does not affect this factor along with its known effect on the thyroid cells (hyperplasia), it can hardly be expected that thiouracil produces more than a temporary remission of the disease. Since the risk of thyroidectomy is now so small, one death in 660 cases, as there is always a risk of developing sensitivity to the drug in spite of continuous observation, and as no great promise of permanent cure from these drugs can be held out for patients with severe degrees of hyperthyroidism, we believe that thyroidectomy following proper preparation is the treatment of choice in hyperthyroidism.

CONCLUSIONS

Experience with the preoperative use of thiouracil, thiobarbital and propyl thiouracil in 660 cases of hyperthyroidism during the last three and one-half years has permitted answers to certain questions regarding these drugs. These drugs act by preventing the synthesis of an active thyroid hormone and by so doing lead to an increase in hyperplasia of the thyroid gland, an hyperplasia similar to, but greater than, that in primary hyperthyroidism. If these drugs are

used in adequate doses over a sufficient length of time no patient will fail to obtain restoration of the basal metabolic rate to a normal level. The comparative dose of thiouracil, thiobarbital and propyl thiouracil is 600 mg., 50 mg. and 200 mg., respectively.

Since the percentage of reactions is mine for thiouracil, 28 for thiobarbital and two for propyl thiouracil, the last named agent is the drug of choice. Since propyl thiouracil may also cause depressive changes in the white blood cells, its administration must be carefully followed with white and differential blood counts made every 10 to 14 days during treatment. The treatment of agranulocytosis consists of the early administration, intramuscularly and by nasal and throat spray, of adequate doses of penicillin.

The time required to restore the basal metabolic rate to normal for complete relief of all hyperthyroid signs and symptoms can be estimated from the type of hyperthyroidism, primary or adenomatous, duration of hyperthyroidism, whether iodine has previously been received, and the size of the thyroid gland. Rapid response occurred in patients with primary hyperthyroidism of short duration without previous administration of iodine (1.3 per cent drop in the basal metabolic rate per day), and slow response occurred in patients with adenomatous goiter when iodine had been administered previously (0.5 per cent drop in the metabolic rate daily). From this information, an individualized program of adequate treatment can be outlined and hospital reservations can be made in advance. Over-treatment with these agents must be avoided since myxedema will result which may increase the surgical risk.

The surgical disadvantage of these drugs in cases of primary hyperthyroidism—increase in vascularity and, therefore, great technical difficulty in carrying out the thyroidectomy—has now been overcome by the use of iodine. Initially, iodine was given during the three-week period before operation but now both drugs are given simultaneously from the start of treatment. The time required for control of hyperthyroidism has not been prolonged and with the rapid immediate benefit from iodine, patients seem to show improvement much sooner than on the plan of giving thiouracil only at the beginning of treatment and adding iodine at the end of therapy.

Initially, only severely hyperthyroid patients were treated preoperatively with these drugs, but now since propyl thiouracil, which has such a low sensitivity rate, is available, we are preparing an increasing number of hyperthyroid patients with this drug. Patients with very mild hyperthyroidism, however, are still prepared with Lugol's solution alone.

These antithyroid drugs do have the capacity to produce prolonged remissions of mild primary hyperthyroidism, as does iodine at times, but little hope can be held for a permanent remission in patients with severe primary hyperthyroidism with a large gland. Since the mortality of thyroidectomy is now almost *nil*, surgical removal after proper preoperative treatment seems to be the treatment of choice for hyperthyroidism.

Lahey Clinic
Boston, Mass.

USE OF THYROID EXTRACT WITH THIOURACIL IN THE PREPARATION OF THE THYROTOXIC PATIENT*

A PRELIMINARY REPORT

RAWLEY M. PENICK, JR., M.D.

NEW ORLEANS, LA.

FROM THE DEPARTMENT OF SURGERY, TULANE UNIVERSITY SCHOOL OF MEDICINE,
AND THE DEPARTMENT OF SURGERY, OCHSNER CLINIC, NEW ORLEANS, LA.

THE INTRODUCTION of thiouracil placed in our hands a valuable drug for the treatment of the thyrotoxic patient. Opinions still differ as to its usefulness in definitive therapy but its advantages in the preparation of these patients for operation are now generally recognized. However, it soon became evident that the drug has certain disadvantages. Chief among these are the length of time required to prepare the patient,¹ the dangerous side-effects sometimes encountered and, lastly, vascularization, hypertrophy and hyperplasia of the gland² which make thyroidectomy technically difficult. This is a preliminary report of an attempt to prevent these undesirable changes in the gland itself and, thus, reduce the technical difficulties during the operation. It is also hoped that this method will shorten the time required for preoperative preparation of the patient.

The hyperplastic changes produced by the administration of thiouracil may have more than one disadvantage. Not infrequently, the size of the gland increases considerably during this therapy and the microscopic appearance is such that at times the pathologist has difficulty in differentiating it from malignancy. All of which has led Hinton and Lord³ to warn against the use of thiouracil in nodular goiter because of its possible carcinogenic effect, where malignancies already tend to occur. One investigator⁴ has been able to produce invasive tumors in animals by giving thiouracil and a carcinogen, but no such results were obtained when one was given without the other.

The increased vascularity and friability brought about by thiouracil was a distinct disadvantage to the surgeon and means were sought to prevent this effect from the drug. As a result, at some stage of preparation of the patient iodine is now given because of its involutionary effect. One group of investigators⁵ believes that iodine can diminish the hyperplasia of the secretory cells even though given at the same time as thiouracil. It is the consensus, however, that under such circumstances the response is delayed and preparation somewhat prolonged. In my experience thyroid glands prepared in this way have been only slightly less vascular than those treated with thiouracil alone, unless the preparation is thorough and prolonged. This difficulty can be remedied if iodine is given ten days or two weeks after thiouracil has been

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

THE THYROTOXIC PATIENT

discontinued. This produces a satisfactory gland but adds to the time required for preparing the patient for operation.

The mechanism by which hyperplasia is produced by thiouracil and other goitrogens is now moderately well understood. In experimental animals this effect of the drug can be abolished by hypophysectomy or the administration of thyroxin.^{6, 7, 8} Iodine does not produce the same result.^{6, 7, 8} For this reason, it is postulated that the circulating thyroid hormone acts as an inhibitor on the pituitary, particularly, as far as the production of the thyrotropic factor. If a goitrogen is administered, a prompt fall in the circulating thyroid hormone ensues; this removes its inhibitory influence on the pituitary gland, which, in turn, responds by increased production of thyrotropic hormone.^{2, 9} The latter is believed responsible for the hyperplastic changes in the thyroid gland (Fig. 1).

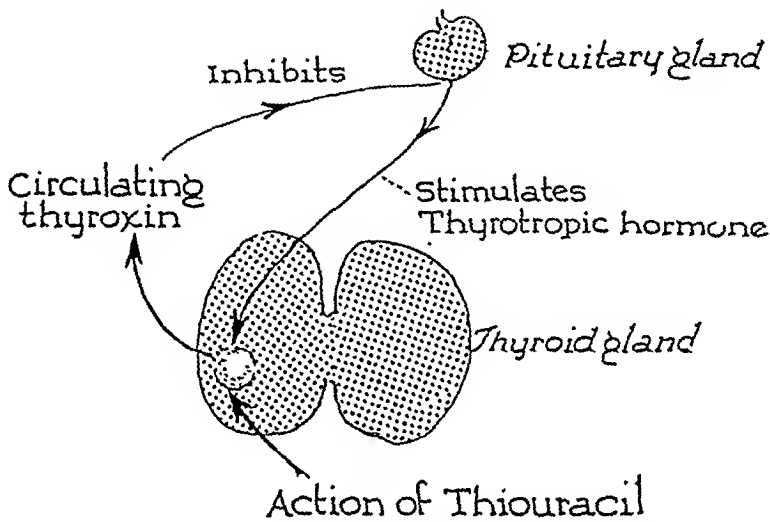


FIG. 1.—Schematic representation of the probable mechanism of the production of hyperplastic changes in the thyroid gland following the administration of thiouracil.

On the basis of the reasoning in the preceding paragraph, thyrotoxic patients were prepared for operation by the administration of both thiouracil and desiccated thyroid. Williams and Clute¹⁰ instituted this regimen in a few patients but apparently it was directed at the exophthalmus. Palmer¹¹ also mentions using thyroid extracts to prevent hyperplasia but gives no results except to state that the administration of thyroxin was found to have no appreciable inhibiting effect on the action of thiouracil in lowering the metabolic rate.

Six patients with classical signs of exophthalmic goiter were prepared for operation by the administration of thiouracil and desiccated thyroid extract. Considerable loss of weight, tachycardia and elevated metabolic rates were evident in all six patients. The average basal metabolic rate on admission for these patients was plus 58. Varying degrees of enlargement of the thyroid gland were present. Thiouracil (0.2 Gm.) was administered three times a day to all patients, and with each dose desiccated thyroid (1 gr.) was also given. In most instances the medications were started on the same day, but in no

case was administration of the thyroid begun longer than one week following the initial dose of thiouracil. These patients received no iodine, as such, at any time.

The preoperative course in each case was satisfactory and was thought to be no different from that of patients who received thiouracil and iodine. A possible exception to this statement was the response shown by the pulse rate but this was hardly significant enough to warrant a definite conclusion except in one instance. This was a middle-aged woman who responded satisfactorily, but the pulse rate decreased more slowly than usual, and following operation pronounced tachycardia persisted for two days. In some instances

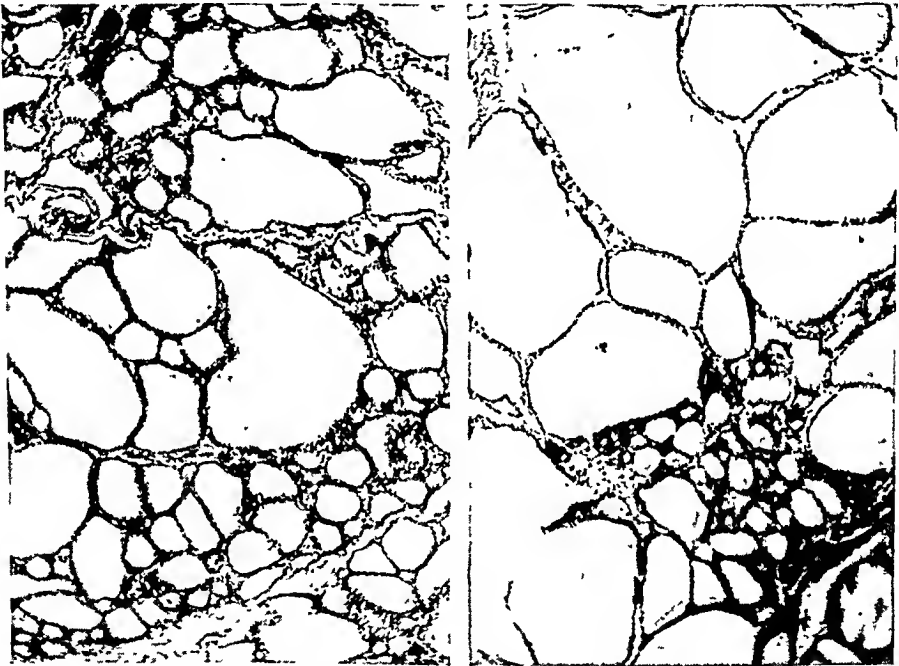


FIG. 2.—Photomicrograph of glands removed from two of the patients treated with both thiouracil and desiccated thyroid, but no iodine. Note the large amount of colloid. (x90)

the thyroid gland became much smaller in size. The average number of days required for preparing these patients was 39.

Thyroidectomy was performed upon every patient. The technical difficulties of the operations were not great. About half of the glands seemed to be no more vascular than those treated in the conventional way with thiouracil and iodine. In the other three cases the gland was perhaps a little more vascular but this was not as great as in those patients whom we prepared by giving thiouracil and iodine at the same time. The postoperative course was uneventful except in the one patient referred to earlier.

Microscopic examination of the removed glands showed satisfactory involution in all (Fig. 2). There was a noticeable increase in colloid, definitely more than is found in untreated exophthalmic goiter, which is usually more

than is found after treatment with thiouracil. The height of the epithelium was never great, although in some instances there were patches of residual hyperplasia sometimes involving only a small tuft in the acinus. It was felt that with more prolonged treatment even this residual hyperplasia would have disappeared.

SUMMARY

Desiccated thyroid was given in conjunction with thiouracil to six patients with exophthalmic goiter, in an attempt to bring about involution of the gland while the patient was being prepared for operation. The pre-operative and postoperative courses were like those noted when thiouracil and iodine are used, except for tachycardia in one patient. Microscopic examination of the removed tissue showed satisfactory involution in all cases. The vascularity of the glands presented no technical problem for the surgeon but the glands were probably not quite as avascular as those treated with thiouracil and then iodine. It is believed that the use of desiccated thyroid offers a satisfactory adjunctive method of preparing thyrotoxic patients for operation.

REFERENCES

- ¹ Astwood, E. B.: Thiouracil Treatment in Hyperthyroidism. *J. Clin. Endocrinology*, 4, 229, 1944.
- ² Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Herman, J., and Cortell, R. E.: Action of Thiouracil upon the Thyroid Gland in Graves' Disease. *J. Clin. Endocrinology*, 4, 1, 1944.
- ³ Hinton, J. W., and Lord, J. W., Jr.: Is Surgery Indicated in all Cases of Nodular Goiter Toxic and Nontoxic? *J. A. M. A.*, 129, 605, 1945.
- ⁴ Bielschowsky, F.: Distant Tumours Produced by 2-amino and 2-acetyl-amino-fluorene. *Brit. J. Exper. Path.*, 25, 1, 1944.
- ⁵ Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O., and Riddell, Charlotte: Effect of Iodine on the Thyroid Gland in Graves' Disease when given in Conjunction with Thiouracil. *J. Clin. Investigation*, 24, 869, 1945.
- ⁶ Higgins, G. M., and Ingle, D. J.: The Relation of the Hypophysis to Certain Changes Induced in the Rat by the Goitrogen, Promizole. *Endocrinology*, 38, 110, 1946.
- ⁷ MacKenzie, C. G., and MacKenzie, Julia B.: Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism. *Endocrinology*, 32, 185, 1943.
- ⁸ Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: Action of Certain Sulfonamides and of Thiourea upon the Function of the Thyroid Gland of the Rat. *Endocrinology*, 32, 210, 1943.
- ⁹ Gordon, A. S., Goldsmith, E. D., and Charipper, H. A.: Thyrotrophic Hormone Content of the Blood Sera and Pituitary Glands of Thiourea-, Sulfadiazine-treated and Thyroidectomized Rats. *Endocrinology*, 36, 53, 1945.
- ¹⁰ Williams, R. H., and Clute, H. M.: Thiouracil in the Treatment of Thyrotoxicosis. *New England J. Med.*, 230, 657, 1944.
- ¹¹ Palmer, M. V.: Hyperthyroidism and Thiouracil. *Ann. Int. Med.*, 22, 335, 1945.

3439 Prytania St.
New Orleans, La.

DISCUSSION.—DR. ELMER C. BARTELS, Boston, Mass.: Doctor Lahey has asked me to limit my discussion to the impressions of the internist regarding the use of these drugs as permanent medical treatment. The objection to their use should not be based solely on the grounds of possible reactions which may follow their use, since I expect that some new drug will be discovered which will have a low toxic incidence, which

requirement propyl thiouracil very nearly fulfills. The objections seem to be more fundamental and can be considered from the pathologic and clinical standpoints. I think there are three or four objections pathologically. First, patients with adenomatous goiters should not be treated with these substances over long periods of time, since there is definite danger of malignant degeneration. Second, in primary hyperthyroidism the hyperplasia which is initially present is increased, so that when the drug is withdrawn the stage is set for a return of hyperthyroidism. Third, the thyroid gland does not decrease in size, although some observers have thought that it does. Certainly, the bruit and thrill remain, and in some instances become accentuated. Fourth, malignant changes might develop in the primary hyperplastic gland, although this, at the present time, is still under discussion. From the clinical standpoint, sustained remission after withdrawal of thiouracil treatment has not been very promising in our experience. Thirteen patients were treated over varying periods of time, over a year in some instances. Irrespective of the length of time, all patients had relapses of the disease. They all had severe hyperthyroidism, with large thyroid glands or large thyroid remnants. Eight patients after withdrawal of treatment have had remissions irrespective of duration of treatment. All had mild hyperthyroidism, with small thyroid glands or small remnants. Most of these patients would probably have reacted similarly to Lugol's solution.

We are at the present time seeing an increased number of patients suffering from relapse of hyperthyroidism to whom thiouracil had been administered before they came to the clinic. Some of these patients could ill afford the effect of delay and uncertainty of thiouracil as a medical therapy and the visceral strain which accompanied recurrent hyperthyroidism. We believe our responsibility to the hyperthyroid patient is one of restoration to health in the shortest possible time and with the least risk, and that these antithyroid drugs, when properly used, with subsequent thyroidectomy, give the patient the best chance of obtaining this end.

DR. ROBERT L. PAYNE, Norfolk, Va.: A single surgeon operating in a small community cannot enjoy the privileged experiences of a large clinic. Yet I have been using thiouracil and propyl thiouracil for about two and one-half years.

Last December I reported the result of 45 cases treated with thiouracil, in five of whom leukopenia developed and was treated by withdrawal of the drug and administration of penicillin. All recovered. We continued the use of thiouracil until about six months ago when propyl thiouracil became available. We have now used this in about 15 cases and have seen no toxic effects. Interestingly enough, some patients who showed leukopenia from thiouracil before we got propyl thiouracil, had no bone marrow reaction whatsoever after being put upon propyl thiouracil.

I particularly arose to take part in this discussion because the carcinogenic effects of thiouracil have been pointed out and, as Doctor Bartels said, these drugs should not be used in the nodular type of goiter lest carcinoma be produced in the adenoma. I have had one case whom I treated with thiouracil that showed carcinoma. Stained sections of tissue were submitted to several outstanding pathologists of this country and all unanimously agreed that the sections showed carcinoma. A report of this case was written up carefully and conservatively, with no implication that the drug produced the carcinoma. The report of the case, together with photomicrographs, was submitted to one of our best surgical journals, and publication of the report was declined. Excerpts of the opinions of five of the editorial board were sent to me, and I agree with them entirely. Their opinions were based on the supposition that the report would create a bad impression and deter the use of the drug in toxic hyperthyroidism. Up to that time there had been no cases reported in the literature following the use of thiouracil. There was one case reported in a discussion on this subject before one of the pathological societies, but this was never reported in detail in any publication. Accordingly, I feel that this case of mine should also be recorded.

The patient was a woman, age 34, with a typical syndrome of hyperplastic hyper-

thyroidism. She was treated with thiouracil 0.6 Gm. daily, and the basal metabolic rate came to normal in about six weeks. She was then given iodine for about ten days and bilateral subtotal thyroidectomy was performed. When the tissue removed was studied, there was an area of carcinoma, about 3 mg. in size, located in the center of both removed lobes. This was not a nodular goiter and was strictly an hyperplastic type. One could easily assume that this patient had carcinoma in the center of both lobes of the thyroid before thiouracil was administered. Yet, one must think in terms of carcinogenic stimulant, since in the tissue removed from this patient there were no adenomata, the areas of carcinoma were located in the middle of each removed lobe, and the area involved was very small.

The patient has remained entirely well since operation, and we have never considered this situation to be one of primary carcinoma. Up to this time, we have not given her any postoperative roentgen ray therapy. In view of the fact that attention has been called to the carcinogenic properties of this group of drugs, I feel justified in relating to you the above-described case of carcinoma, but do not feel that one case would justify any definite implications against the drug administered.

DR. HAROLD L. FOSS, Danville, Pa.: All of us interested in the problem of hyperthyroidism and its treatment are grateful to the three essayists for what they have told us regarding their experiences in the use of these new and remarkable drugs.

In discussing thiouracil with my staff I recently remarked that, because of severe complications following the use of this substance, the government must soon remove it from the market, and, therefore, was interested in hearing Doctor Lahey make something of the same statement. While it is almost specific when properly used, and with the patient under observation, it is a dangerous drug and possesses unpredictable potencies. Our incidence of agranulocytopenia has been high, with about 30 per cent of cases showing leukopenia. We have refused to accept patients unless they came regularly to the laboratory every ten days for a blood count or arranged to have it performed by their own physicians, who were prepared to report promptly to us any change in the white cells. Such complications, of course, are a thing of the past now that we have propyl thiouracil. As Doctor Bartels stated, there may yet be some other antithyroid drugs synthesized that will eliminate the 2 per cent of complications characteristic of propyl thiouracil. I was glad to hear Doctor Lahey state that we are now safe in using propyl thiouracil routinely in all cases of hyperthyroidism and as a preoperative measure.

May I refer for a moment to a group of patients who are benefited by propyl thiouracil and thyroidectomy, and about whom but little has been written. I refer to those patients with "exophthalmic goiter" yet without goiter. These patients are not problems so much of therapy as of diagnosis. In a review of 3,000 consecutive patients operated upon by the speaker, we found that approximately 8 per cent with definite hyperthyroidism had no goiters, or had glands that, when resected, weighed less than the 30-40 Gm. usually considered as normal in weight and size for adults.

A recent group of 96 consecutive patients with advanced hyperthyroidism and without thyroid enlargement, was studied. All had glands, on resection, weighing less than that of the normal adult thyroid. The average weight was 23 Gm. The average age was 38; the average duration of symptoms was slightly over 12 months. Many had been treated as heart cases and for years. Many had been on digitalis interminably. All had the classical evidences of hyperthyroidism except for the presence of goiter.

(Slides were shown of a number of illustrative patients with advanced hyperthyroidism, with markedly elevated basal rates, exophthalmos, sinus tachycardia, *etc.*, yet without goiters.) These patients constitute an important group of toxic thyroid cases, patients who may readily be cured following propyl thiouracil treatment and thyroidectomy, yet are frequently overlooked because of the absence of a goiter.

DR. HOWARD MAHORN, New Orleans, La.: It would be an obvious advantage if patients could be prepared in a short period of time and brought to the same stage of

safety as if they were prepared over a long period of time. In 44 patients operated upon on my service since preoperative thiouracil and iodine in combination were used, 15 had a basal metabolic rate of over 50; eight were over 75, and one had an initial basal metabolism of +100. All were prepared and operated upon in three weeks. No stage-operations were done, and there was no mortality. One was operated upon when she had a metabolic rate above +50. This means that after the use of thiouracil and iodine the criteria of operability is entirely different from that when iodine alone is used. A patient with a rate of +35 after treatment with thiouracil and iodine is probably in the same risk-stage as a patient with +20 prepared with iodine alone. It may be possible to prepare many of these patients quickly in a short period of time with safety and yet without the necessity of waiting for the basal metabolism to reach an absolute normal. I realize that this is a small group upon which to base this conclusion, but it brings up this possibility which may be worth consideration.

DR. WARREN H. COLE, Chicago, Ill.: When the antithyroid drugs were introduced, most of us, including surgeons, were interested in the question as to whether or not patients with hyperthyroidism would be removed from the practice of surgery. Although I am convinced that hyperthyroidism should be eliminated before thyroidectomy is performed, I am of the opinion that thyroidectomy will be indicated in the great majority of cases; thyroidectomy will be unnecessary in only a small portion of cases. In a small series of about 30 cases followed by us at Illinois Research Hospital, longer than eight months after cessation of six to eight months drug therapy, we noted that almost 50 per cent have shown no evidence of recurrence. Offhand, that appears favorable, but I suspect this impression is erroneous, because if we wait long enough many will come back with recurrences. In general, the recurrences occur in those who had great toxicity, and the good results in those with mild toxicity and small glands. In reality this was a picked group, insofar as it contained a large number of patients with mild toxicity.

In patients with nodular goiter I believe there is a distinct danger of development of carcinoma if the goiter is left in place year after year. A recent study we made at Illinois Research Hospital revealing a much higher incidence of carcinoma in nontoxic nodular goiter than in toxic nodular goiter, has led me to this fear.

In closing, I want to make a plea that we not consider the thyroid problem as being solved, and not forget all the things we have learned the hard way in the last two decades. Twenty-five years ago the operative mortality was as high as 4 to 6 per cent, but it is now less than 1 per cent. It dropped because we applied an improved knowledge of physiology to our treatment. I want to call attention particularly to the necessity of improved nutrition as a prerequisite in preoperative preparation. Hyperthyroid patients must show a gain in weight before operation can be considered. The patient who comes to the hospital in crisis cannot be relieved by antithyroid drugs. Until the day arrives when a drug is found which will neutralize the thyroid hormone, we will have to struggle along in these patients with crisis with the knowledge possessed before antithyroid drugs were introduced. Until such a drug is found that patient will remain a problem; for this reason alone, we must not discard all the knowledge it has taken us two decades to accumulate.

However, I do wish to congratulate Doctor Astwood, and his associates, for their epochal and most valuable contribution to the problem of hyperthyroidism.

DR. WILLARD BARTLETT, St. Louis, Mo. (closing): It has been 45 years since my first trip to Rochester, Minnesota, on which occasion the great Will Mayo made one remark I shall never forget, particularly apropos to this subject. He said: "Our trouble is not that we do not know enough about surgery; our trouble is that we do not use our knowledge." So my plea tonight is that those who are interested follow those six criteria of operability I threw on the screen, and if all are adopted and met satisfactorily, there will be practically no deaths in crisis.

DR. FRANK H. LAHEY, Boston, Mass. (closing): I would like to add one or two points which we have learned. We have learned that it is wise to omit propyl thiouracil for seven or eight days before operation. We have seen agranulocytosis occur seven days after the last dose was given, and it would be undesirable to have agranulocytosis at the time of operation, during the time of wound-healing or in the presence of possible wound infection. For that reason we have omitted it during the last week.

The reason Doctor Bartels was pushed into using iodine and propyl thiouracil together throughout the treatment was because of crises or thyrocardiac cases which still come to us, and he has seen such patients under thiouracil alone become worse. We, therefore, want something more prompt than the delayed action of thiouracil, and that is iodine.

These patients can do anything during their period of preparation for the operation. They take it at home. They are not incapacitated. Their white cell and differential counts are forwarded to us by their family doctor.

When we first began to prepare these patients for operation, we thought if we got their metabolic rates lowered that, while they were not normal, the patients were good surgical risks and we could operate upon them and so save them time. That we have not found to be true. The degree of thyroid reaction is something that cannot be predicted and we have had dangerous reactions in inadequately prepared cases so that only hemithyroidectomies could be undertaken safely. Everyone knows that an occasional patient who looks to be a good risk will have an unexpected reaction, and such an occasional patient will die. Therefore, we urge very strongly that propyl thiouracil be administered until the metabolic rate in these cases is completely normal. By this plan we can be sure that there will be no reaction and, with the complication rate as low as it is with propyl thiouracil, in our opinion there is no excuse to submit these patients to operation until all the toxicity has been completely abolished.

The following example of such a complicated case is one that I have repeatedly employed. This is one of our personal friends, a woman, age 77, with a metabolic rate of +48, a weight loss of 35 pounds, and the presence of auricular fibrillation, moderate decompensation and diabetes. Under propyl thiouracil the basal rate was restored to normal, auricular fibrillation was abolished, compensation restored, the diabetes put under easy control. She was then submitted to operation and, following subtotal thyroidectomy, never had a pulse rate above 80. Had this patient been operated upon before being made completely nontoxic, it could, I believe, have been a completely different story.

As to whether or not iodine involutes these glands perfectly, there can be no question. We could not have prepared 660 cases with thiouracil or propyl thiouracil and iodine and not have brought about satisfactory operating conditions. All of us who operate upon these patients at the clinic have now done so many thyroid operations that if some of them had bled excessively or the technical difficulties had been great, we would immediately have heard complaints about them, and there have been none. I can assure you that the preparation of these patients with Lugol's solution will so involute the thyroid gland that they will be as satisfactory to operate upon when prepared with propyl thiouracil and iodine as patients with hyperthyroidism were when they were prepared solely with Lugol's solution.

DR. RAWLEY M. PENICK, JR., New Orleans, La. (closing): I would like to comment on Doctor Lahey's statement about involution with iodine. I think iodine will bring about involution. On the other hand, I have operated upon some patients given iodine simultaneously with thiouracil, and the gland was vascular and friable. I think probably the reason for this is that the patients did not have it long enough. I think it is possible to get a very satisfactory gland with iodine.

AN EVALUATION OF PULMONARY EMBOLISM FOLLOWING INTRAVASCULAR VENOUS THROMBOSIS*

JOHN J. MORTON, M.D., E. B. MAHONEY, M.D.,
AND G. B. MIDER, M.D.
ROCHESTER, N. Y.

FROM THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, NEW YORK

THE MANY VARIATIONS in the management of thrombosis and embolism have prompted us to review our 20 years' experience with these conditions. We have compiled our statistics from the records of the Strong Memorial and Rochester Municipal hospitals. The protocols of the 1,752 surgical autopsies have been carefully analyzed. The autopsy figures are accurate, but we are sure that the clinical records are incomplete owing to the inadequate recording and filing during the war years. This will weight our statistics toward the fatal side. Undoubtedly, many minor pulmonary emboli have been overlooked, especially those with vein ligation and recovery. Our principal effort has been directed towards evaluating those factors which seem to predispose to pulmonary embolism, both fatal and nonfatal.

Age.—In studying age distribution it is apparent that fatal pulmonary embolus is most common in surgical patients over 50 years of age. The 6th, 7th and 8th decades are the most unfavorable for the surgeon. The medical patients present a slightly earlier grouping, the majority being 40–70 years. This is without doubt due to the heart disease of rheumatic origin in the medical deaths in this northern part of the country (Figs. 1, 2, Table I).

Sex.—There were no significant differences in sex distribution.

Time of Postoperative Embolus.—Approximately 80 per cent of postoperative pulmonary embolism occurs in the first two weeks (Fig. 3).

Heart.—A factor of prime importance which stands out clearly is the condition of the heart. If the cardiac action is impaired by heart disease there is danger of a slowing of the peripheral venous circulation. Weakness of the cardiac muscle, incomplete valve closure, irregularities in cardiac rhythm may lead to congestion in the lung bases and in the peripheral circulation. Increased hydrostatic pressure and venous stasis offer ideal situations for the development of intravascular clotting. Clots form at stasis or eddy points wherever there is compression of the vessel wall from without, especially in the elderly. Patients in coma often have embolism as they lie completely immobile for long periods. This has a bearing on the frequency of embolism in brain cases. It probably accounts for a number of fatalities in the urologic group where uremia is so prevalent. On the basis of autopsy figures the

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

evidence shows that the heart weight is materially higher in the patient with fatal pulmonary embolism. Taking 400 Gm. as the upper limit of the normal heart, the incidence of cardiac hypertrophy is much higher among patients with pulmonary embolism than in the group in whom no emboli were found. When one considers anatomic evidence of cardiac decompensation as found at postmortem the differences are even more striking (Table II). The influence

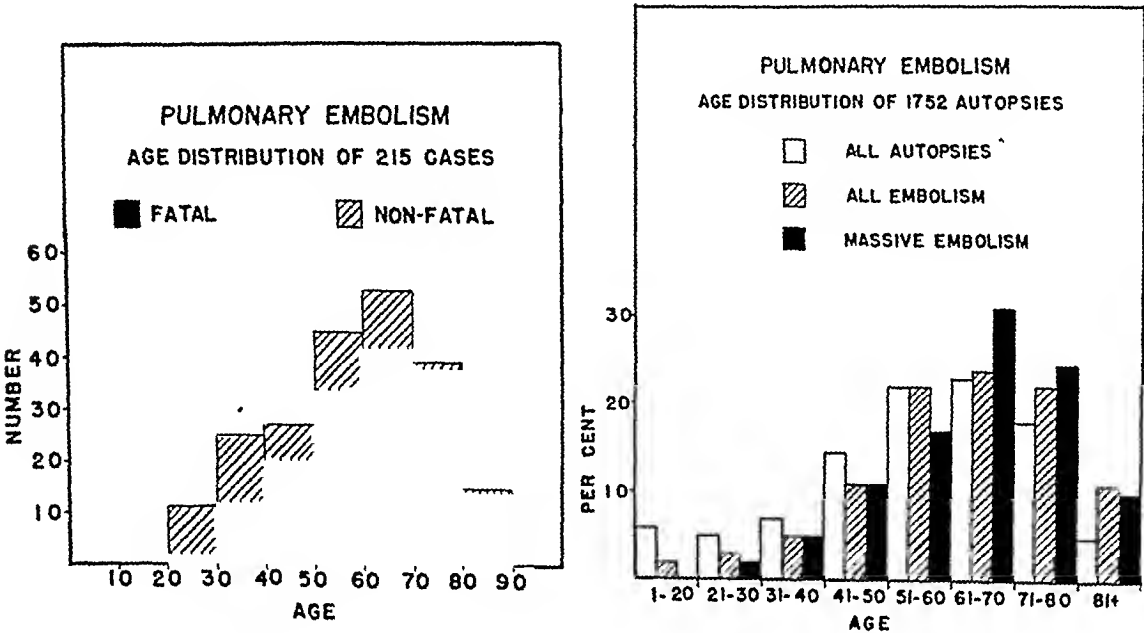


FIG. 1

FIG. 2

FIG. 1.—Age distribution of 215 cases of pulmonary embolism found in 1,752 autopsies.
FIG. 2.—Age distribution of 1,752 autopsies in relation to age distribution of all pulmonary emboli and massive (fatal) pulmonary emboli found at necropsy.

TABLE I
FATAL PULMONARY EMBOLISM IN MEDICAL AND SURGICAL PATIENTS
Age Distribution

Years	Medicine Number	Surgery Number
10-19.....	4	0
20-29.....	3	2
30-39.....	12	12
40-49.....	27	20
50-59.....	31	34
60-69.....	60	42
70-79.....	36	38
80+.....	5	14
Total.....	178	162

Includes patients who had neither operations nor clinical evidence of thrombophlebitis.

of heart disease is even more strikingly evident in the clinical study of pulmonary embolism. Forty-one per cent of the patients who survived after one or more pulmonary emboli had no heart disease. Only 8 per cent who had any evidence of heart disease survived. No patient survived a pulmonary embolus who had cardiac decompensation (Table III).

Mobilization.—It has always been the policy in our hospitals to mobilize patients early. Older patients have been made ambulatory within 24 hours of operation whenever possible. We have been able to do this because our wounds usually have been sutured with silk and, thus, can withstand early strains. We did this as far back as 1928 with the idea of avoiding hypostatic pneumonia. One of our conclusions at that time was: "Mobilization of the aged patient without undue concern about the incision seems to be a factor of safety in preventing postoperative complications."⁶ We consider it just as important

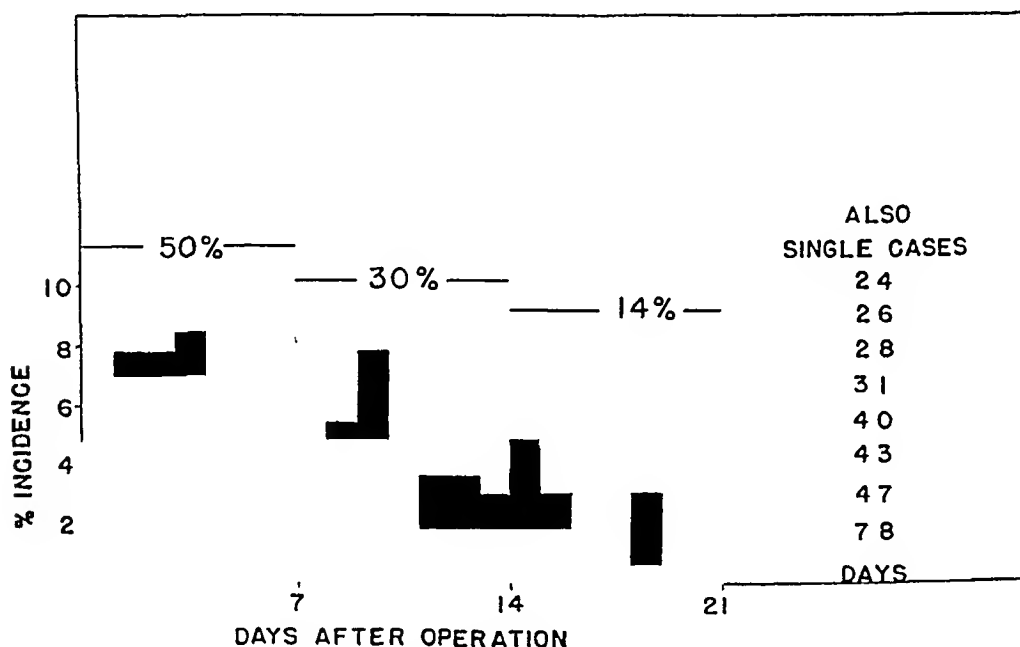


FIG. 3.—Day of occurrence of postoperative pulmonary embolism in 168 cases.

to mobilize the patient in bed by means of exercises, frequent turning, hyperventilation and by encouraging him to change his position. This is not possible in a heavily sedated patient. We prefer to have our patients on the uncomfortable rather than the too comfortable side. Early ambulation often means a short period of standing with assistance or sitting in a chair. While this is important it only occupies a small fraction of the day. The patient's own muscular exertion is the variable that is important.

Position.—Position in bed may be a factor of importance in contributing to peripheral venous stasis. The common practice of propping up the knees by the mechanical breaking of the bed and the similar elevation of the head and trunk,—the so-called "jack-knife position,"—would appear to favor puddling at the ankles and femoral—inguinal creases, with subsequent impairment of venous return. The popliteal and femoral inguinal creases would contribute definite points of pressure on the vascular channels. All together if the

position be maintained for a few hours it constitutes a definite hazard. In contrast to this, if the lower limbs were elevated by raising the foot of the bed so that the limbs were about 15° above the horizontal, drainage from the vessels would be promoted, there would be an increase in the volume blood flow into the caval circulation, and stasis would be prevented. The head could be raised to a comfortable level at the other end of the bed,—a matter of 15° – 20° usually (Fig. 4).

TABLE II
CARDIAC STATUS IN RELATION TO PULMONARY EMBOLISM

	1752 Autopsies		
	No Emboli	Small Emboli	Large Emboli
Trauma:			
Number of observations.....	235	32	14
Mean weight hearts.....	355	370	425
Hypertrophied hearts.....	25%	31%	57%
Failure.....	8%	28%	28%
Appendicitis:			
Number of observations.....	40	5	2
Mean weight hearts.....	340	365	445
Hypertrophied hearts.....	28%	25%	2
Failure.....	15%	20%	0
Peptic Ulcer:			
Number of observations.....	69	13	2
Mean weight hearts.....	360	330	405
Hypertrophied hearts.....	22%	23%	50%
Failure.....	17%	39%	50%
Intestinal Obstruction:			
Number of observations.....	66	10	2
Mean weight hearts.....	365	350	375
Hypertrophied hearts.....	27%	20%	50%
Failure.....	20%	40%	100%
Benign Prostatic Hypertrophy:			
Number of observations.....	74	23	19
Mean weight of hearts.....	425	450	435
Hypertrophied hearts.....	47%	57%	74%
Failure.....	24%	22%	53%
Gangrene:			
Number of observations.....	46	13	7
Mean weight hearts.....	380	400	420
Hypertrophied hearts.....	39%	43%	43%
Failure.....	13%	61%	71%
All Autopsies:			
Number of observations.....	1432	199	121
Mean weight hearts.....	325	360	390
Hypertrophied hearts.....	21%	28%	39%
Failure.....	16%	27%	28%

Position on the operating table may also be criticized especially in urologic, gynecologic and rectal operations. Here, the tendency to put patients in stirrups with flexed knees and hips for fairly long periods may well be instrumental in starting the intravascular clots which manifest themselves as emboli later. It is our custom following operation where this position has been used to completely extend the legs at the knees and to elevate the whole limb to the vertical at the same time gently stroking over the veins to empty them.

Other Factors.—There are many other factors which probably influence intravascular clotting, such as paralytic ileus, obesity, dehydration and varicose

veins. We have attempted to evaluate these in our clinical studies of pulmonary embolism and their incidence is tabulated. (Table IV) An incidence of 38 per cent of paralytic ileus in the fatal emboli may well be significant but we have no comparable standards for reference. We were surprised to find that only 10-12 per cent of our patients with pulmonary embolism had varicose veins.

We have found that infection is present in 75 per cent of our cases with embolism, whether fatal or nonfatal. By infection we refer to any type of

TABLE III
INFLUENCE OF HEART DISEASE ON PULMONARY EMBOLISM

	Nonfatal	Fatal
No heart disease.....	41%	59% (100 cases)
All heart disease.....	8%	92% (98 cases)
Cardiac decompensation.....	0	100% (57 cases)

TABLE IV
FACTORS INFLUENCING PULMONARY EMBOLISM

112 Cases. 29 Living, 83 Fatal

	Nonfatal		Fatal	
	Present %	Absent %	Present %	Absent %
Infection.....	72	28	76	24
Paralytic ileus.....	31	69	38.5	61.5
Obesity.....	17	83	28	72
Dehydration.....	3.5	96.5	18	82
Varicose veins.....	10.5	89.5	12	88

bacterial invasion of the body, such as pneumonia, genito-urinary tract infection, peritonitis, septicemia, cellulitis, wound infection, gangrene of extremities, empyema, *etc.* It is by no means necessary that infection be in the immediate neighborhood. Infection is known to cause increased coagulability of the blood, and because of this is probably a potent factor in thrombosis.

Lesions which Predispose to Pulmonary Embolism (exclusive of gynecologic conditions).—The common lesions encountered in autopsies on surgical patients are presented in Table V. The gross incidence of pulmonary embolism is 17 per cent, while 6.5 per cent of all patients had large emboli which occluded one or more major branches of the pulmonary artery. All emboli that possibly might have originated in the right heart have been eliminated from this series. The patients with benign prostatic hypertrophy, uncomplicated herniae, gangrene of the extremities and carcinomas of the colon and rectum have by far the highest incidence of fatal pulmonary embolism. Patients suffering from severe traumatic injuries have an average number of embolic episodes, but it is probably significant that almost all of the fatal pulmonary emboli were found in old ladies with fractured hips. It is interesting

that no fatal pulmonary emboli were found among those patients who died from complications of ulcerative colitis and esophageal carcinomas. Brain tumors deserve especial mention since the incidence of fatal pulmonary embolism exceeded that of the entire series. Probably none of these were suspected clinically.

A summary of our clinical experience with pulmonary embolism is recorded in Table VI. The ratio of fatal to nonfatal embolism is highest in operations on the brain and genito-urinary system. It is interesting to note that the same proportion of patients survived pulmonary embolism after gynecologic surgery as they did after abdominal surgery.

FIG. 3

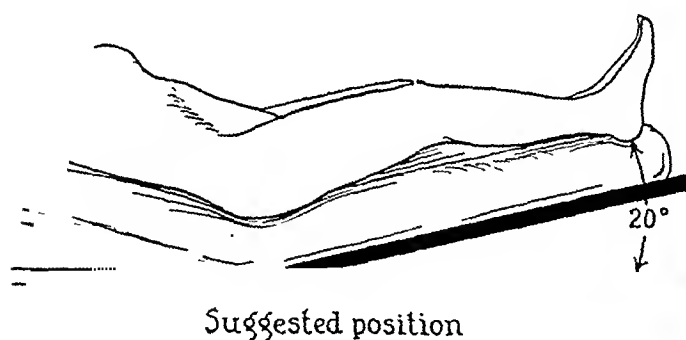
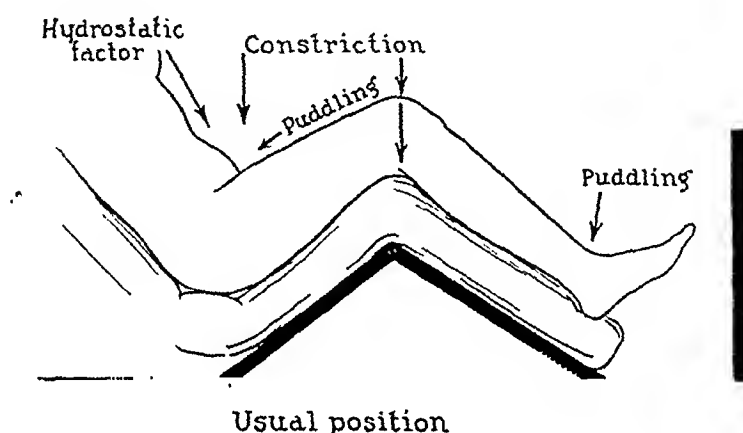


FIG. 4

FIGS. 3 and 4.—Demonstrating the usual and the recommended methods of adjusting the bed.

None of our patients are known to have survived pulmonary embolism after a brain operation, major amputation, or abdominoperineal resection of the rectum. There have been five instances of pulmonary embolism following ligation for varicose veins. There has been one fatality following such an operation. There has been one fatality by pulmonary embolism following bilateral therapeutic ligation for phlebothrombosis and at least one where non-fatal emboli have occurred following ligation.

Sources of Emboli.—The Swiss and German investigators^{3, 5} have given rather conclusive evidence that the majority of the thrombi from which emboli occur are to be found in the legs. As early as 1934, Homans¹ pointed out the importance of these observations, and suggested prophylactic and therapeutic vein ligation in pulmonary embolism. At the present time there seems to be rather general agreement in this country among both surgeons and pathologists that the legs furnish the main source for the emboli. The postmortem examination as done in America really contributes very little to the knowledge of the source because of restrictions against dissecting the extremities. It is

TABLE V
PULMONARY EMBOLISM IN RELATION TO COMMON SURGICAL LESIONS
1752 Autopsies

Lesion	No Embolism		All Embolism			Massive Embolism			
	No.	Mean Age	No.	Incidence	Mean Age	No.	Incidence	Mean Age	Massive/All
Appendicitis.....	55	42	10	15%	60	4	6%	55	40%
Peptic ulcer.....	65	60	16	20%	57	2	2.5%	79	13%
Intestinal obstruction.....	77	59	13	14.5%	64	2	2%	69	15%
Infection.....	250	50	45	15%	55	7	2.4%	59	16%
Colitis.....	18	47	7	28%	52	0	0	0	0
Pancreatitis.....	18	58	5	22%	66	1	4%	75	20%
Trauma.....	229	52	47	17%	70	16	6%	74	34%
Gangrene.....	49	63	22	31%	70	7	10%	62	32%
Gallstones.....	76	61	13	15%	59	6	7%	55	46%
Hernia.....	15	58	5	25%	67	3	15%	67	60%
Benign prostatic hypertrophy	81	71	42	34%	74	20	16%	73	48%
Other genito-urinary.....	47	56	11	19%	58	5	8.6%	56	45%
Carcinoma stomach.....	62	61	16	20.5%	59	5	6%	53	31%
Carcinoma colon and rectum	108	62	26	19%	63	13	10%	68	50%
Carcinoma bladder.....	38	65	6	14%	63	2	5%	57	33%
Carcinoma prostate.....	69	69	16	18.5%	75	7	8%	74	44%
Carcinoma pancreas and biliary system.....	50	60	7	12%	57	4	7%	59	57%
Brain tumors.....	96	43	17	14%	49	9	8%	49	53%
Carcinoma esophagus.....	26	60	2	6%	71	0	0	0	0
Other neoplasms.....	143	55	26	15%	61	3	2%	57	12%
Other diseases.....	63	50	9	12.5%	60	6	8%	55	67%

apparent that fatal emboli come from the larger veins, and previous small warning emboli are probably an early stage of the thrombotic process in smaller veins.

Neither our clinical nor our autopsy experience contributes a great deal to the knowledge of the source of pulmonary emboli, but indirect evidence makes us agree with the present-day theory. We now feel that it is unlikely that fatal pulmonary emboli have their origin from smaller thrombosed veins about an operative site. When embolism occurs from such a site, it usually consists of multiple small septic thrombi. When there is no evidence that the legs or the pelvic veins are involved, the heart is probably the source. We have been amazed that patients receiving continuous intravenous therapy, who have many superficial veins of both arms and legs thrombosed, rarely have

PULMONARY EMBOLISM

pulmonary emboli. The only incidence of pulmonary embolism which we could attribute to intravenous therapy resulted after using varicose veins of the leg as the only available situation for intravenous therapy. This occurred in a patient with extensive burns of the trunk and upper extremities. The introduction of blood was followed by two nonfatal emboli and a subsequent phlebitis.

Case No. 216681.—A 46-year-old electrician was readmitted to Strong Memorial Hospital a few minutes after receiving electrical flash burns of the face and hands. His clothing had caught fire and burned his arms, neck and trunk. At the time of admission shock had not yet become clinically evident. Examination revealed second-degree burns of the face and hands and extensive third-degree burns of the trunk and arms. The burns were treated with compression dressings, and plasma was given intravenously. After the first day, he received daily whole blood transfusions and intravenous Amigen. Because no arm veins were available leg veins were used for intravenous injection and at times

TABLE VI
PULMONARY EMBOLISM
Type of Operation

	Living	Fatal	Dead of Other Causes
Neurosurgery (brain)	0	6	2
Genito-urinary.....	6	32	0
Bone and joint.....	3	11	2
Abdominal.....	15	31	7
Abdominoperineal resection rectum.....	0	4	4
Thyroid.....	1	2	0
Drainage abscess.....	1	7	1
Amputation.....	0	9	0
Ligation of veins.....	6	1	0
Gynecologic.....	8	18	0
Total.....	40	121	12

it was necessary to use varices of the legs. Thrombophlebitis developed in the right leg on the 10th hospital day. On the following day he developed signs of a left pulmonary infarct. Three days later there was an episode of pain in the right chest. Because of the very extensive phlebitis, vein ligation was not considered feasible, so anticoagulant therapy with heparin and dicumarol was started. No further emboli occurred and skin grafting of the third-degree areas was accomplished without difficulty. The phlebitis had subsided at the time of discharge.

THE PROBLEM

Our present method of therapy has been based on the following impressions which we have gained from our own past experience, and that of others: (a) We consider clinical thrombophlebitis a dangerous situation, and it is a warning which should not be ignored, as there is a 25 per cent chance of pulmonary embolism.¹ In thrombophlebitis there is a 6 per cent chance of a fatal outcome.¹ Recently, there has been a tendency to feel that once phlebitis has become established there is very little danger of a thrombus breaking loose in the blood stream as an embolism. In our experience, we have

seen patients who have had repeated pulmonary emboli, some of them fatal, at a time when phlebitis was definitely present. We realize that the embolus may have arisen from the normal leg rather than from the involved one. Consequently, in dealing with this problem we believe that a bilateral ligation should be done. We formerly used diodrast to help us in deciding what to do, but this has been abandoned because we were unable to interpret venograms correctly, and the diodrast is perhaps irritating to the veins. (b) When there has been a pulmonary embolism, even though there may be no gross clinical involvement of the legs, this warning *must* not be ignored. There is a 44 per cent chance of a subsequent embolus, and an 18 per cent chance of a fatal one.¹ In some instances there may be minimal clinical signs which will lead one to suspect the involved extremity, but in others repeated examinations by experienced individuals have failed to elicit pain, tenderness, or a positive Homans' sign. Under these circumstances we now believe that bilateral femoral exploration and ligation should be performed.

Case No. 154980.—A 61-year-old woman was admitted to the Strong Memorial Hospital on February 9, 1944. She had a breast carcinoma for which a radical mastectomy was done on February 15, 1944. She was out of bed sitting in a chair on the 4th postoperative day. Her wound healed without infection. The stitches were removed on the 7th postoperative day. On the next day, at 1:00 P.M., she had an acute episode which was diagnosed as either a pulmonary embolus or a coronary occlusion. Signs of pulmonary infarction became definite at the right base. Repeated examinations of her legs gave no indication of phlebitis. She was kept in bed, and improvement was progressive until March 9, 1944, when she had a second episode, and an increased area of involvement in the right lung. She still showed no evidence of phlebitis. On the 33rd postoperative day, she had pain in her left leg for the first time. Under local anesthesia, both femoral veins were ligated above the clots which were present in each. One hour after operation she complained of severe pain in the left chest, became cyanotic, went into shock, and died shortly thereafter. Postmortem examination showed pulmonary emboli with pulmonary infarction. There were thrombi in the right iliac veins. Microscopic sections showed these to be antemortem clots.

We are not yet convinced as to the proper treatment for the patient who complains of minimal tenderness in the calf, and who has not had a pulmonary embolus. Perhaps this would be the type of patient who would be benefited by heparin and dicumarol. Our experience with these drugs has not been sufficient to answer this question. Barker's¹ report, however, would seem to support this therapy.

The rationale for the ligation of the major veins of the extremities or the vena cava in patients who have presented neither thrombosis nor embolic phenomena must next be considered. This procedure is based on the presumption that a certain percentage of such individuals will ultimately have thrombosis and embolism. The therapy is regarded as a prophylaxis against such a complication. As there is no way of determining which side may be the offender, bilateral femoral ligation must be done. It is logical to make it a single higher ligation, namely, the vena cava, as it also covers the possibility of thrombosis arising in the large pelvic veins. It also gives a chance for

better collateral circulation as the ligation is higher. As far as we can determine no one has considered ligation in continuity, with the chance of later recanalization. It is probably not done because of fear of overlooking loosely attached clots above the ligature. Objections to tying the normal vena cava are that it calls for a major-type operation, that swelling and discomfort of the legs are produced for an indefinite period, and that the pain of this distention may require sympathetic blocks or sedation. Some writers claim that pain and inflammatory reaction are relieved by the temporary interruption of the sympathetics running along the vein walls. This has not been the experience of most surgeons. No one has emphasized the fact that after division of a major vessel, with ligation, thrombosis is the natural healing process, the thrombus propagating itself up to nearest branch. This being so, the surgeon can have no comfort that his therapy will prove effective. The problem is simply transferred to a higher level if the underlying causes for the condition have not been corrected. We have not tied the veins on patients who do not show either thrombosis or embolism because we believe that it is too radical surgery. Too many veins would be tied unnecessarily to ward off danger in too few patients.

Surgical intervention in suspected cases of phlebothrombosis is bound to damage the venous return from the legs in a large proportion of cases. Probably the majority of these suspects do not actually require surgical intervention but, as of today, it seems impossible to evaluate the potentialities of a given case. In other words, surgical therapy for phlebothrombosis is unsatisfactory but is being forced on the attending surgeon.

The problem of phlebothrombosis can only be solved by further investigation of the physicochemical aberrations of the venous circulation in the patient who is put to bed. We need more information regarding the mechanism of venous return from the legs; on the maintenance of venous pressure; on the blood clotting mechanism; and on the viscosity and the wetting power of the blood. Pulmonary embolism is by no means an exclusively surgical problem. The best position to take on any adult patient who must be confined to bed is that he may be a potential candidate for thrombosis and embolism. Measures should be promptly put into effect to minimize these possibilities. These measures are active mobilization by means of stated exercises at stated periods; maintenance of cardiac efficiency if possible; hydration; minimal sedation and elevation of the legs above the cardiac level. Successful prevention depends on active coöperation of all medical attendants as well as of the patients themselves.

REFERENCES

- ¹ Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M.: The Use of Dicumarol in the Prevention of Postoperative Thrombosis and Embolism: With Special Reference to Dosage and Safe Administration. *Surgery*, 17, 207, 1945.
- ² Dennis, C.: Disaster Following Femoral Vein Ligation for Thrombophlebitis, *etc.* *Surgery*, 17, 264, 1935.
- ³ Dock, W.: Use and Abuse of Bed Rest. *N. Y. State J. M.*, 44, 724, 1944.

- ¹ Homans, J.: Thrombosis of the Deep Veins of the Lower Leg Causing Pulmonary Embolism. *New England J. Med.*, 211, 993, 1934.
- ² Hunter, W. C., Krygier, J. J., Kennedy, J. C., and Sneed, V. D.: Etiology and Prevention of Thrombosis of the Deep Leg Veins. *Surgery*, 17, 178, 1945.
- ³ Morton, J. J.: Surgical Care of Patients in the Extremes of Life. *Am. Jour. Surg.*, n.s., 30, 92, 1935.

260 Crittenden Blvd.
Rochester, N. Y.

DISCUSSION.—DR. ARTHUR W. ALLEN, Boston, Mass.: I would like to congratulate Doctor Morton on this survey of his experience because it is basic and because it coincides almost identically with our own experience at Massachusetts General Hospital, in an analysis of this problem made several years ago. I cannot give an account of all our studies in this discussion, but I want to emphasize that the management of the problem as a whole should be definitely divided into two categories. One is that of prophylaxis; in suitable cases that may be antieoagulant therapy. This is very effective but it must be carried out under strict laboratory control. The other method of prevention is to admit that, in patients with certain lesions, beyond a certain age, the chance of embolus is very great, and that prophylactic interruption of the deep veins of the leg is a logical procedure. The other chief consideration is that of treatment after thrombosis or infarct has occurred.

Up to October 1st of this year we have treated by bilateral femoral vein interruption 1,060 patients, after infarct or after definite leg signs have been noted. In five of these patients who had had sublethal emboli before femoral vein interruption, subsequent emboli produced death. In addition, in the older age-group, we have interrupted the veins prophylactically in 458 cases. There have been five instances of mild phlebitis and one fatal embolus in this series. In 458 patients, as nearly similar as we could determine as to age, sex, trauma, type of operation, illness, *etc.*, without prophylactic femoral vein interruption, there were 55 instances of phlebitis and 26 fatal emboli. This I think is significant.

I wish to stress, at this time, that in none of these more than 1,500 patients subjected to bilateral femoral vein interruption in our hospital has there been any loss of life or loss of limb as a result of the operation. Furthermore, I wish to say that we have found that interrupting the normal vein caused practically no sequelae of any importance. This interested us a great deal; they did not develop thrombophlebitis and swelling afterward, as we feared they might. We feel that this prophylactic attack in the vulnerable age group is justified.

There were 110 cases in each group with fracture in or about the hip. In the 110 cases that had prophylactic interruption there were two instances of mild phlebitis and no fatal embolus. In the immediately preceding 110 cases there were 20 instances of phlebitis and 11 fatal emboli. It has been known for a long time that cases with injuries to the leg are particularly prone to develop thrombosis and embolism. In 49 leg amputations where prophylactic interruption was done, there were no instances of phlebitis and no emboli; whereas in the control group of 49 there was one phlebitis that was recognized and six deaths from pulmonary embolism. In gastrectomy in this age-group, in 48 cases there were nine instances of phlebitis in cases not interrupted and three fatal emboli. In 20 cases of hernioplasty that had prophylactic interruptions, one fatal embolus occurred. We think there might have been an error in technic in the interruption of the veins in this case. In 20 cases of the same type there were three instances of phlebitis and one fatal embolus.

There were 20 cases of decompensated heart disease in each group. Our medical men are quite different, apparently, from those in Rochester. We are sometimes embar-

passed by their insistence on having this procedure done; they frequently say please do it, rather than asking our opinion about its necessity.

We believe that prophylactic dicumoral is suitable for patients under 60 years of age who had no contraindications to its use. We think that prophylactic femoral vein interruption is logical and safe for patients beyond the age of 60.

Treatment may be of three types: femoral vein interruption, anticoagulents and lumbar sympathetic procaine blocks. These may be used alone or in conjunction, depending upon the indications.

DR. FREDERIC W. BANCROFT, New York, N. Y.: Early mobilization, in the hands of most of us, has not been as successful as it might have been. All have seen cases of phlebothrombosis and embolism develop in patients mobilized early. To some of us this meant having the patient out of bed and sitting in a chair. If you will visualize the picture that Doctor Morton showed, with the patient in the Gatch position, you will recognize how much worse it is to have a patient sitting in a chair, feet down, and the patient quiescent. There is a pressure on the popliteal space and acute flexion at Poupert's ligament associated with venostasis. Actually, early mobilization should be that a patient gets out of bed and walks. When tired, he should return to bed, with the bed nearly flat. While in bed, he should constantly utilize his legs in active motion, as described years ago by Doctor Pool.

There is another type of phlebothrombosis which originates in the pelvic veins and not in the superficial and deep veins of the leg, as described by Doctor Allen. In order to emphasize my points I should like to mention briefly two cases:

Case 1.—A woman who had had a cesarean section followed by a normal convalescence. She went home on the 10th day postoperative. Four days after her return home, she had sudden pain in her chest, with an elevation of temperature. She was readmitted to the hospital. On radiologic examination, it was difficult to determine whether her symptoms were due to virus pneumonia or an embolism. There was no pain nor swelling in either thigh or leg. Nine days later, this patient developed evidence of deep thrombosis on the left side. I was called in to see her and operated, and sucked out a thrombus from the iliac vein. The suction apparatus did not work well and I was not satisfied that I had removed the entire thrombus. Following this procedure the patient was better, but on the 9th day following she had a sudden attack of pain in the right chest and again evidence of an infarct by radiologic examination. I did a thrombectomy on this side. The patient, however, succumbed from the involvement of the chest. On postmortem examination, there was found a thrombus from the left side protruding about two inches upward into the vena cava; there were massive emboli in both lungs. Microscopic examination of the uterus showed that the pelvic veins were the cause of the original phlebothrombosis. They had extended into the iliac vein and were not noted in the thigh until the retrograde thrombosis had extended downward.

COMMENT.—It might have been better in this case, if the patient had not been so desperately ill, to have ligated the vena cava.

Case 2.—This patient was a young woman who had had a normal pregnancy. Eight days following delivery she had pain in the left chest and radiologic evidence of a probable infarct. Both thighs and legs were normal on examination. With the memory of the previous case in mind, we operated simultaneously on the femoral veins under local anesthesia just under Poupert's ligaments. On opening the veins, no clots were detected but each vein was in definite spasm. A sucker was passed up for a distance of about eight inches in each vein, and thrombi were removed by suction until free bleeding returned. With the exception of the fact that the patient needed immediate transfusion due to blood loss, her convalescence was uneventful and she returned home on the 9th postoperative day.

COMMENT.—Obviously in this case the thrombus had started in the pelvic veins.

I still believe that the study made by Dr. Stanley-Brown and me some years ago indicates that there are potential intravascular clotters as well as potential bleeders. At that time we made a routine examination of the prothrombin and fibrinogen of all antepartum and postoperative cases. We felt that everywhere in the body are *hyper* and

hypo conditions, such as hyperthyroidism, and hypothyroidism, hyperacidity and hypoacidity. Therefore, if there are potential bleeders, there must be potential clotters. In our analysis of about 1,600 cases we found that about 14 per cent were potential clotters. All our accidents occurred in this 14 per cent, but these accidents constituted only 2 per cent of the 14 per cent. On analyzing the remainder of the 14 per cent, we found that they had a rather prolonged convalescence, in that the temperature remained slightly elevated and there was evidence of some malaise, and we assumed that some of these might have been deep thromboses which we did not recognize.

It would be a great help to us all if we knew pre-operatively which cases were likely to develop a postoperative accident. While I recognize that the prothrombin test is not as accurate as it might be, I still believe that it may be an indication of the potential patient who may develop phlebothrombosis.

DR. WALTER D. WISE, Baltimore, Maryland: I want to say a word about prophylaxis, not from an operative standpoint but from the anticoagulant viewpoint. I want to make a preliminary report of an intensive study of the use of dicoumarol in my hospital which has been going on for some years as a therapeutic measure, and more recently as a prophylactic. There will be a paper published which includes only surgical patients, not including the medical cases that have been spoken of. The results lately, since we have been using dicoumarol prophylactically, are so good that we hesitate to bring them out because I know that no such record as this can be maintained. It is possible that the good results are not due to dicoumarol alone, but to a combination of procedures such as has been outlined.

In Mercy Hospital in Baltimore, 4,000 to 4,500 operations are performed in a year, including deliveries but excluding nose and throat cases. In the four-year period from 1939 to 1942, inclusive, there were 50 cases of postpartum and postoperative thrombophlebitis, 22 cases of pulmonary infarction and eight deaths. In 1943 the use of dicoumarol was begun. From 1942 to 1946 there were 41 cases of thrombophlebitis with 13 pulmonary emboli and four deaths. In 1944 a rather intensive program of prophylactic use of dicoumarol was started. The staff has cooperated very well and it has become almost routine. The chief of the laboratory is willing to work long hours, and does, and is very much interested in it, and the results are that in 1945 only six cases were diagnosed as thrombophlebitis, and so far in 1946 there have been six. In 1945 there was one pulmonary embolus, two so far in 1946, and no deaths in those two years. That record can hardly be maintained. It may be coincidental, to some degree, but it does give, in a medium-sized service, some reason to pay a little more attention to anticoagulant prophylaxis and therapy than is being done, according to what we have heard today.

DR. ROY D. McCLURE, Detroit, Mich.: Recently we had a symposium on this subject at the Sectional Meeting of the American College of Surgeons in Detroit. One of the speakers was Dr. Gunnar Bauer, of Sweden. He presented the results of heparin therapy in two Swedish hospitals, and the statistics indicated that the drug was of value in the prevention of fatal pulmonary embolism. He stated that he preferred heparinization rather than femoral vein ligation. There is great interest in heparin among the Swedish doctors. Dr. Eric Jorpes, of Stockholm, who is in this country at the present time, has just published a revised and enlarged edition of his monograph on heparin.

At the Henry Ford Hospital, we have used the anticoagulants and vein ligation. Dr. Conrad Lam and Dr. Donald Hooker have recently published the statistics on our cases (ANNALS OF SURGERY, 123, 221, 1946). They found that since the adoption of anticoagulant therapy and prophylactic femoral vein ligation, there has been a very low mortality rate in cases selected for treatment. However, these measures did not prevent a number of sudden and unexpected embolisms. They thought that early ambulation offered the most promise as a preventive measure easily applicable to most surgical patients.

DR. ROLLIN A. DANIEL, JR., Nashville, Tenn.: Dr. Richard Crutcher and I are completing a study of this problem at the Vanderbilt University Hospital, based on clinical and autopsy records over a 15-year period, 1930 to 1945. During this time there were 82,984 admissions to the hospital; 30,000 operations were performed; 2,749 autopsies were performed, representing 63 per cent of the patients who died in the hospital during that time.

Among the autopsy cases there were 55 in which pulmonary embolus was probably the cause of death. Nineteen of these patients had more than one embolus. Thirty-six patients had a single massive embolus.

The 55 autopsy cases were divided into two groups as follows:

1. Those patients who could not have recovered from their disease had pulmonary embolism not occurred. There were 21 patients in this group. Ten of these had cardiac failure which could not be controlled by adequate digitalization and all other supportive measures; seven had far-advanced malignant disease; one had severe tetanus, two widespread abdominal and pelvic infections, with septicemia, and one had bilateral congenital cystic kidney with pyelonephritis and uremia. All these patients were in the terminal stages of their disease.

2. Those patients who probably would have recovered had pulmonary embolism not occurred. There were 34 patients in this group. Analysis of this group revealed that six patients had massive edema involving the extremities, caused by hypoproteinemia or nephritis. Clinical evidence of intravascular clotting would have been extremely difficult to detect in these patients. There were, therefore, only 28 patients in whom phlebothrombosis might have been noted and in whom one might have been willing to perform operative procedures designed to prevent pulmonary embolism.

We feel that it is important to emphasize the fact that more than a third of the fatal emboli occurred in patients with incurable diseases.

DR. JOHN J. MORTON, Rochester, N. Y.: I wish to thank all the discussants for the kind way they have handled me. What I meant to emphasize is that this is not an exclusively surgical problem by any means. It is a problem of putting patients to bed. If your patient is an adult, he will get thrombosis if you keep him there and do not take measures to prevent it. Early ambulation is a good thing. In most cases this may mean a few steps and then back to bed. We wish to stress that the exercises in bed are more important. These keep the muscles in tone and the veins drained.

We may come to tying normal veins, but we have not done it yet, and I want to see a few more indications before we do.

THE STUDY OF MALIGNANT CELLS WITH PHASE DIFFERENCE MICROSCOPY*

W. M. FIROR, M.D., AND G. O. GEY, M.D.

BALTIMORE, MARYLAND

MODERN SURGERY has made significant contributions to the welfare of patients afflicted with malignant disease, but modern surgery has made no significant contribution to our understanding of malignant processes. The efforts of pathologists in this field have been similarly futile. For more than thirty years living cells have been observed and recorded photographically, without giving any insight into those essential physiologic alterations that constitute malignancy. For many years biochemists have tried to detect some significant variation between normal and malignant tissue. Their efforts to find some qualitative abnormality commensurate with the abnormal behavior of malignant tissue have failed. Quantitative differences between benign and malignant tissue have, however, been described, and during the past three years exceedingly significant changes have been noted in the field of enzymology. Biochemists for more than 15 years have given us a series of carcinogenic components, but the action of these substances upon intracellular constituents is not fully understood. Efforts to correlate chemical alterations with cellular structure are just beginning to bear fruit. Midway between the realm in which the chemist works and that of the microscopist lies a zone which, heretofore, has not been open to scrutiny. I refer to those intracellular components which are larger than molecules and yet too small to be seen by the ordinary light microscope. During the past three years two technics have been started which permit observation and study of these intracellular constituents.

The first of these new methods is electron microscopy. The work of Porter, Claude,¹ and others, has already enlarged our knowledge of intracellular structure, and in the next few years one can reasonably expect many important additions to this knowledge. The second technic is phase difference microscopy, and it is this technic which we shall briefly describe and illustrate this morning. Suffice it to say, the essential feature of this method consists of altering the contrast in the image by introducing in the microscope a diffraction plate which changes absorption and optical path differences. The advantages of phase difference microscopy are great when one deals with homogeneous material, such as cytoplasm. This presentation is not a verbal description, but a visual demonstration of what can be accomplished by this method. I would like to point out that in the early part of the film I am about to show.

* The authors wish to thank the American Optical Company for furnishing them with phase contrast equipment.

Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

one can see the movement and behavior of the cell membrane. Heretofore, this has not been clearly seen with the ordinary light microscope.

It is suggested that you focus your attention on the following features of this plasma membrane that surrounds every cell within the body. It is flexible, it is contractile, it is tenacious, and it is porous. The amazing fact is that, when a cell divides, the cell membrane remains intact. The second feature to which I direct attention are certain components of the cell which, heretofore, have not been visualized in living tissue, particularly the network in the central cell mass and the Golgi apparatus. Finally, in the last portion of the film one can see the behavior of certain cell constituents. In particular, I refer to the movement of the mitochondria which shuffle back-and-forth from the edge of the cell to the central cell mass. This is particularly significant when one remembers that recently it has been shown that the mitochondria contain nearly all of certain respiratory enzymes.³

(Motion Picture)

This presentation is in no way exhaustive. It has served merely to give us a glimpse into the possibilities of a new technical procedure and to show the way we are thinking, and possibly give a suggestion as to the direction in which we are heading.

REFERENCES

- ¹ Porter, K. R., Claude, A., and Fullam, E. F.: *J. Exp. Med.*, 81, 233, 1945.
- ² Bennett, A. H., Jupnik, H., Osterberg, H., and Richards, O. W.: *Trans. Am. Mic. Soc.*, 65, No. 2, April, 1946.
- ³ Hogeboom, G. H.: *J. Biol. Chem.*, 162, 739, 1946.
Hogeboom, G. H., Claude, A., and Hotchkiss, R. D.: *J. Biol. Chem.*, 165, 620, 1946.

The Johns Hopkins Hospital
Baltimore, Md.

DISCUSSION.—DR. WALTMAN WALTERS, Rochester, Minn.: I think we should all commend Doctor Firor for this excellent research of a type which few of us are in position to carry out but which he and his associates have done admirably.

As a member of the National Advisory Cancer Council I bring to your attention something which I think you should know. In 1937, Congress created the National Cancer Institute. The appropriation for this Institute has varied from \$400,000 to \$570,000 each year, until the current fiscal year in which it was increased to \$1,772,000. These figures are used for the support of the National Cancer Institute and the various grants-in-aid recommended by the National Advisory Cancer Council. Dr. George Smith of New Haven, Dr. Frank Adair of New York, Doctors Ivy and Huggins, Dr. Sherwood Moore of St. Louis, Dr. Robert Stone of San Francisco and I are members of the committee which meets with the Surgeon-General of the United States Public Health Service and with Dr. R. R. Spencer of the National Institute of Health. This agency operates the National Cancer Institute in which some of the investigations of cancer are being carried out. Other studies are being made in leading medical institutions of this country. These monies are available for use in the study of any problem associated with cancer.

Some of you may say that you have not sufficient trained personnel in your hospitals

to carry out investigations of cancer. You will be interested in knowing of the type of grants requested and that many of the studies needed could be carried out by any of us. For example, studies dealing with (1) the frequency with which gastric polypi become cancerous; and (2) the incidence of cancer in presumably benign gastric lesions as well as in the presence of atrophic gastritis are being carried out in one institution. At a recent meeting of the Western Surgical Association, Lt. Col. Frank E. Hamilton, of Walter Reed Hospital, presented a report of the effect on the stomach of roentgen therapy applied to the abdomen for treatment of metastatic tumors of the testis. Chronic perforating gastric ulcers resulted.

Studies of this type can be carried out by all of us if we have the opportunity. We were told that in the next session of Congress, as a result of demands from people all over the country, an appropriation of \$100,000,000 will be sought for the study of cancer. The plan is to bring scientists from all over the world to the United States in an effort to correlate and to further projects of research on cancer in accordance with plans to be developed by these men in a manner similar to that used in invention of the atomic bomb.

My suggestion would be that those who desire to carry out research on cancer do something which we, as scientists and doctors, find difficult to do; namely, request our senators or representatives in Congress to see that this money is wisely spent, make suggestions as to the types of research on cancer that might be carried out and request grants of money for support of such studies in our medical schools and hospitals. I should like to encourage all who have any desire to do research on cancer to make inquiry of the National Advisory Cancer Council as to what monies are available for such purpose.

DR. JOHN C. A. GERSTER, New York City: Now that the country has become cancer-conscious there is much danger of confusion and duplication of effort. The hundred million dollar Bill mentioned by Doctor Walters is a good example of this because, while authorizing appropriation of this sum for the commendable object of gathering scientists from all over the world to attack the cancer problem, it seems so loosely written—lacking any proper directive provisions—as to be almost a blank check and, thus, open to great political distortion. Obviously for this reason the Bill is now being rewritten.

The government is fighting cancer; I understand some \$200,000 of federal money is available for New York State alone. The American Cancer Society also has substantial funds allocated for cancer work in this same territory. A year ago the American Cancer Society, whose three-fold object is research, service and education, collected four and a quarter millions from all over the country. They engaged the National Research Council of the National Academy of Sciences' Committee on Growth to pass on all research problems submitted and to recommend action on these back to the American Cancer Society. There are 19 separate panels of the Committee on Growth to conduct and supervise research on every aspect of the cancer problem.

This year the American Cancer Society's campaign grossed more than 11,000,000 dollars.

Now for some of the confusion: The National Cancer Institute of the U. S. Public Health Service is located at Bethesda, Maryland, with Dr. Roscoe Spencer as its head; on the other hand, the National Cancer Foundation is a well-intentioned organization directed mainly toward terminal care of the advanced cancer patient. While this is a most worthy charity, it, alone, is not going to solve the main problem. To concentrate everything on advanced cancer care is like pouring money down a rat hole. This well-intentioned movement should not be confused with more worthy organizations which, *while including advanced cancer care in their programs*, stress the clinical and basic research aspects of the cancer problem as the only path toward the light!

DR. CHAMP LYONS, New Orleans, La.: I am sure we are all filled with admiration for this magnificent achievement in pathologic research. One of the most remarkable

aspects of this accomplishment is the opportunity provided for testing new drugs as competitors with essential metabolites in the enzyme systems of neoplastic cells. Doctor Firor has carried the technic to a high degree of perfection. I should like to ask him to briefly outline his technic.

DR. WARFIELD M. FIROR, Baltimore (closing). I want to thank Doctor Walters and Doctor Gerster for their timely remarks. I heartily endorse everything Doctor Gerster said about the need for thinking clearly and not confusing these various agencies. In answer to a question asked me personally, as to the speed at which these exposures were taken, one can say that this varies according to cell activity; roughly one exposure every $\frac{1}{10}$ second. Many times one has to watch a cell for four or five hours before it begins to divide.

In answer to Doctor Lyons; I think I might make clear the essentials of phase microscopy by using the blackboard. If one has a light source here, and here an object; here is the microscope with the objective lens, and here the resulting image. This image will be altered by certain variables or variations in the components of the object. First, the ability of different parts of the object to transmit light; second, the thickness of the components of the object; third, the index of refraction of these components. If in this object there is a highly refractile granule, that will be reflected in the image. The product of the thickness times the index of refraction divided by the wave length is called optical path. The optical path, expressed in wave lengths γ is equal to nt/γ where t is thickness and n is the index of refraction of the structure. When optical path differences between adjacent parts of the object are very great, one can get a sharper image by dark-field illumination. When, however, there is very slight difference in the thickness or in the index of refraction of material that goes to make up the object, one can not detect these differences with the ordinary light microscope, and under these conditions phase microscopy is particularly helpful. This method consists of putting into an objective lens a disk of glass on which there has been evaporated a metallic or dielectric material which absorbs some of the rays of light, or deflects them. Some 60 different plates have been devised.

Obviously, the possibilities of this method are very great. For a technical presentation of phase microscopy one is referred to a paper by Bennett,² *et al.*

SURGICAL CONSIDERATIONS IN THE TREATMENT OF HYPERTENSION*

WINCHELL McK. CRAIG, M.D.,

DIVISION OF NEUROSURGERY, MAYO CLINIC,

AND

KENNETH H. ABBOTT, M.D.,

FELLOW IN NEUROSURGERY, MAYO FOUNDATION,

ROCHESTER, MINNESOTA

THE SURGICAL TREATMENT of hypertension by means of extensive sympathectomy and splanchnicectomy has been accepted as a sound and logical physiologic procedure. It is true that abnormal elevation of the blood pressure may persist for years in a mild degree without producing symptoms or disability, so that neither medical nor surgical treatment is indicated. More severe elevation of blood pressure may respond to medical management and remain under control without proving disabling or showing evidence of progression. In reviewing reports relating to the surgical treatment of hypertension, one is struck with a universal problem confronting the medical profession; namely, the control of progressive hypertension or the alleviation of distressing symptoms of an already severe and serious hypertension.

Various types of sympathectomy have been carried out and studied extensively, both preoperatively and postoperatively, and from these we have learned much about what can be accomplished by each type of procedure. In contrast to many operations performed on man which have as their principle the removal of pathologic tissue, the operative treatment of hypertension is based on a physiologic response of the patient; that is, interruption of the sympathetic fibers will abolish or diminish the increased arteriolar tone in the lower half of the body. As Grimson¹ has stated, the lowering of the blood pressure observed to follow sympathectomy has been directly proportional to the extent of the sympathectomy and inversely proportional to the severity of the disease.

CLASSIFICATION

Due to the fact that the clinical syndrome which we have come to recognize as hypertension has no single etiologic factor and that elevated blood pressure associated with arteriolar changes may result from many combinations of causes, it is necessary to have a clinical classification as a basis for evaluation of therapeutic results and for prognosis. Several classifications have been developed by the various workers in this field, based on the apparent clinical and pathologic evidences of the severity of the disease. All classifications have a common objective in evaluation of the severity of the disease as well as in the selection of patients whose condition should respond satisfactorily to surgical treatment.

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

Hypertension may be divided into two main groups: (1) secondary; and (2) essential or primary hypertension. Secondary hypertension results from such lesions as glomerulonephritis, pyelonephritis, obstruction of the urinary tract, rare conditions obstructing a renal artery, polycystic disease, terminal periarteritis nodosa and disseminated lupus, coarctation of the aorta and tumors of the suprarenal and pituitary glands.

It is not our purpose to discuss this group at length; however, it seems advisable to call attention to the unilateral renal lesions, usually atrophic pyelonephritis (contracted kidney), which may be causes of hypertension. This type of lesion is of importance to the surgeon, since there are an increasing number of reports of favorable responses to removal of such lesions. However, these favorable responses actually are comparatively rare.

When this lesion has been suspected, it is customary at the Mayo Clinic to have a combined operation performed by the urologic and neurologic surgeons, the operation consisting of nephrectomy and sympathectomy. The two operations can be carried out through the same incision without materially increasing the operative risk. If definite and persistent lowering of the blood pressure occurs after removal of the kidney, further surgical treatment (sympathectomy on the opposite side) is not necessary. In such circumstances removal of the kidney is given credit for the lowering of the blood pressure, for it is known that unilateral sympathectomy does not materially lower the blood pressure for more than a few days. If, a week or ten days after removal of an atrophic kidney is performed in association with sympathectomy, there is no decrease in blood pressure, it is assumed that the kidney is not the sole etiologic factor, and a secondary operation is then considered necessary. The patient is then regarded as having primary or essential hypertension.

ESSENTIAL OR PRIMARY HYPERTENSION

Etiologic Factors.—Not much is known about the mechanism of elevation of the blood pressure in the presence of essential hypertension. Three factors are responsible for maintenance of normal blood pressure, and derangement of any one of these may cause a change in the blood pressure. The factors in question are: (1) the cardiac output; (2) the volume and viscosity of the blood; and (3) the resistance offered to the flow of the blood through the peripheral parts of the arterial system. It has been proved that cardiac output or viscosity of the blood is not altered in cases of essential hypertension, but that the caliber of the peripheral vessels is decreased. The decrease in diameter of the peripheral vessels is attributable to (1) a condition inherent in the arterioles; and (2) an abnormal reaction of the arterioles to vasomotor stimuli. Wide fluctuations of blood pressure would be indicative of an abnormal response of arterioles to vasomotor stimuli. A high sustained blood pressure with little fluctuation would be indicative of an inherent or automatic constriction of the arterioles.

There is a large hereditary factor in essential hypertension, as revealed by Ayman² (1934), who found that in families in which both parents had absolutely normal blood pressure, the incidence of elevated blood pressure among

the children was only 3 per cent. In families in which one parent had hypertension the incidence increased to 28 per cent, and in families in which both parents had arterial hypertension the incidence was 45 per cent. Hines and Brown³ have shown that a familial history of hypertensive cardiovascular disease is five times more frequent among persons who have hypertension or, who are hyperreactive to a standard stimulus (immersion of the hand in ice water) than it is among persons who react normally to the test. The exact inherent quality responsible for this is not known, but probably a hyperreacting sympathetic nervous system responds abnormally and produces unusual vasoconstriction as a result of various emotional stresses and strains. This, in turn, may lead to so-called neurogenic hypertension.

Classification of Primary or Essential Hypertension.—We have assumed that in any attempt to assess the value of an operative procedure for hypertension, the results of surgical treatment must show a decided improvement over those of medical treatment. Because, since 1932,⁴ a classification has been used at the Mayo Clinic in the diagnosis and medical treatment of hypertension, we have used this classification as a guide and yardstick in evaluation of our surgical results. Keith, an internist, and Wagener, an ophthalmologist, with the collaboration of members of the sections on vascular diseases and pathologic anatomy, have followed an unusually large number of patients suffering from hypertension over a period of two decades or more and have accumulated, therefore, a vast amount of clinical and pathologic material on the basis of which their classification has been developed.

They have classified essential hypertension into four groups.⁵ To avoid the use of descriptive terms, the groups have been given numbers: (1) slight to moderate increase in the blood pressure, which ordinarily becomes normal as a result of rest, and mild sclerosis of the retinal arteries, usually without symptoms (Fig. 1a); (2) moderate to severe hypertension, moderate sclerosis of the retinal arteries, and occasionally venous thrombosis; clinical symptoms are present or absent (Fig. 1b); (3) moderately severe hypertension and angiospastic retinitis with an exudative retinopathy almost always associated with clinical symptoms of hypertension (Fig. 1c); and (4) severe hypertension, angiospastic retinitis, edema of the optic disks and, always, clinical manifestations of hypertension (Fig. 1d).

This grouping does not indicate the degree of hypertension, although the blood pressure is often higher in one group than in the group which numerically precedes it. The hypertension of any patient may progress from group to group until Group 4 is reached. The fatality rate among patients who have hypertension of Group 1 or Group 2 is 30 to 42 per cent, respectively, within four years. The fatality rate among patients who have hypertension of Group 3 is 78 per cent within four years, and in Group 4 the rate is 98 per cent (Keith, Wagener and Barker⁶). This high fatality rate should be noted carefully by those who are inclined to consider that hypertension ordinarily is not a serious disease. Malignant hypertension and essential hypertension are not separate conditions, for malignant hypertension is a type of essential hyper-

tension. The term "malignant" is used loosely to designate severe forms of hypertension.

This classification may be unsatisfactory because it fails to indicate the importance of the rapidity of progression of the disease. As a working basis, however, the classification is acceptable, since the seriousness of hypertension ordinarily increases progressively as the number of the group into which it is classified increases. Thus, to be of clinical value, the surgical treatment of hypertension must show control of the progress of the disease from one group to another, or a lessening in the severity of the hypertension.

Medical Treatment.—The medical treatment of mild essential hypertension usually is satisfactory, but severe hypertension frequently may not respond to medicine and diet. Some patients who have moderate hypertension of Group 2 or 3 respond rather well, for a time, to medical treatment. A nontoxic, adequate and prolonged vasodilator would solve the problem of the treatment in many cases. The nitrites, acetylcholine series, histamine and two newer drugs, tetra-ethyl-ammonium chloride and the bromide salt of this compound, have in common a vasodilating action. The latter two drugs are now under investigation to determine their efficacy from the standpoint of selection of patients for surgery and the medical treatment of hypertension. Due to their temporary physiologic effect, their therapeutic value is questioned. There is some evidence that potassium thiocyanate may be effective (both before and after operation), but the dosage must be carefully regulated. The sedative agents, particularly the barbiturates, are the most valuable drugs. The amount of sedative drug should be great enough to abolish nervousness and restlessness and small enough to avoid drowsiness and excessively slowed mental reactions.

Surgical Treatment.—Although it is true that mild hypertension may persist for many years without evidence of progression, there are a large number of patients who come for surgical treatment after their condition has progressed to severe hypertension, with irreversible changes in the vascular tree of the heart, kidneys, brain and other organs. As was the case in the treatment of cancer 20 years ago, under the present setup we are attempting to alleviate symptoms produced by organic changes far beyond the scope of physiologic surgery. To us the answer thus far is early surgical attack, and our results in hypertension of Groups 1 and 2 as compared with those in hypertension of Groups 3 and 4 for the most part substantiate this recommendation.

Selection of Patients.—The postoperative results have revealed that a high fixed hypertension associated with diffuse arteriosclerosis is accompanied by irreversible changes throughout the body. Patients thus afflicted are not materially benefited by operation. For this reason, certain criteria have been sought by means of which it will be possible to predicate the postoperative results. Observation of the patient at rest and of his response to anesthesia, as well as sedation with the barbiturates, have been tried with varying results. Comparison of the results obtained in the various groups of hypertension, both before and after operation, have shown that patients suffering from severe hypertension in the later stages of the disease may not display marked clinical

improvement after surgical treatment. It is the consensus that patients more than 50 years old with a high diastolic pressure should be looked on as poor operative risks for whom only questionable results can be obtained. Patients who have maintained a high pressure over a long period of time often prove refractive to surgical treatment. It has been found experimentally and clinically that the blood-pressure-altering effect of rest, sedation and anesthesia has been variable. Causative factors or surgical prognosis based principally on rest and the use of sodium amytal or the results of anesthesia tests may be misleading.⁷ The blood-pressure-lowering effect of these tests clinically should be but one of the many factors considered in evaluation of the condition of the hypertensive patient.

Types of operation for hypertension are listed in Table I.

Surgical Operation.—The multiplicity of operations⁸⁻¹⁷ which have been tried and the controversy which has been aroused in respect to the application and results are testimony, in themselves, that one procedure has not proved to be infallible.

All operations for the relief of essential or primary hypertension have a basic physiologic objective consisting of denervation of the vascular tree of the abdominal viscera and the lower extremities. All operative procedures take cognizance of the fact that failure results if both cardiac and renal functions are significantly impaired. Irreversible changes in the vascular, muscular and nervous systems, as well as in the cardiac, renal and other vital organs, indicate a condition which is not amenable to this physiologic type of operation.

Thus far, in review of the results of operation in the treatment of hypertension, it is evident that two types of responses are significant. In one group of cases there has been a definite control of the progression of the disease as evidenced by a lowering of both the systolic and the diastolic pressure for varying periods. In another group there has been a decided relief of the distressing and disabling symptoms without a startling lowering of the blood pressure. This is true in spite of the definite objective of lowering the blood pressure primarily and relieving the symptoms secondarily.

In the acquisition of experience with the different operative procedures, with careful preoperative and postoperative studies of the patients and a longer period of observation, much has been learned, and it is important to realize that the surgical treatment has brought out many hitherto unknown physiologic facts about the disease.

In view of the fact that all the procedures in question have been followed by some alleviation of elevated blood pressure and symptoms and are attended with a low fatality rate (with the exception of the several types of rhizotomy^{8, 9} which have been abandoned), it is barely possible that they can be used individually in the treatment of various phases or stages of hypertension. This has proved to be true in many controversial operative surgical procedures in general surgery and the other surgical specialties. In fact, in our combined medical and surgical departments we have discussed this problem and are, at the time of this report, comparing the results of various operations in the hope



FIG. 1 (A) —Diffuse arteriolar disease with hypertension of group 1, generalized narrowing of grade 1, and chronic sclerosing of grade 1 of the retinal arterioles; (B), diffuse arteriolar disease with hypertension of group 2, generalized narrowing of grade 1, and chronic sclerosing of grade 2 of the retinal arterioles; (C), diffuse arteriolar disease with hypertension of group 3, retinopathy without papilledema, a cotton-wool patch and hemorrhage and residues of edema in the retina; (D), diffuse arteriolar disease with hypertension of group 4, retinopathy with papilledema and partial macular star. (Original colored photographs from the collection of Drs. H. P. Wagener and C. W. Rucker and reproduced through their courtesy.)

of clarifying this question. However, it will take a longer period of observation and study of the patients who have undergone the more extensive sympathectomy before any valid conclusions can be made.

Surgical Technics.—So much has been written concerning the different technics that it seems unnecessary to refer to them in detail. So many contributors have been involved that, in the hope of presenting a brief review, we have assumed that too many names would confuse the subject.

Suffice it to say that rhizotomy extending from the 6th thoracic nerves to the 2nd lumbar nerves was carried out with the idea of interrupting the sympathetic impulses to the splanchnic vessels and the vessels of the lower extremities.⁸ Physiologically, this was sound, but the procedure also involved the motor components of the spinal nerves, which only beclouded the picture, and the operation proved to be of such magnitude and to be accompanied by so much risk, not only of life but of physical disability, that it was abandoned as being surgically hazardous. However, before this procedure was abandoned, it was modified to involve the 9th thoracic nerve to the 2nd lumbar nerve, instead of the original 6th thoracic nerve to the 2nd lumbar nerve.⁹ Some gratifying results were obtained from the latter procedure without the extensive operation and the risk of the former. This showed that in some cases a modified procedure was effective.

The various types of rhizotomy, having proved that interruption of the sympathetic impulses to the splanchnic area was followed by a lowering of the blood pressure and a relief of symptoms, aroused the interest of neurosurgeons in approaching the problem from extraspinal route, and from this interest two procedures developed. Intrathoracic supradiaphragmatic resection of the 10th, 11th and 12th thoracic sympathetic ganglia and the intervening trunk, along with a corresponding section of the splanchnic nerves, has been carried out and several large series of patients have been followed for a period of years.¹² The results as reported are impressive, in respect to both lowering of the blood pressure and alleviation of symptoms.

The subdiaphragmatic operation, consisting of removal of the splanchnic nerves and the 1st and 2nd lumbar sympathetic ganglia with the intervening trunk, has been carried out in large series, with results which show a definite advance in the surgical treatment of hypertension.^{10, 11} The patients concerned have been studied both preoperatively and postoperatively over a period of years, and the results of such studies prove without a doubt that in some cases there has been a definite physiologic response to this type of denervation.

Under this impression—that both the supradiaphragmatic and the subdiaphragmatic types of resection of the splanchnic nerves and the sympathetic ganglia had their advantages, and that more extensive denervation probably would be followed by a greater response—the two procedures were combined into the transdiaphragmatic type of surgical procedure.¹³ This procedure has been modified by several surgeons^{14, 17} until now it has been accepted as a procedure which may be applicable to a group of patients whose condition did not respond as well as had been hoped for when the other procedures were

used. The first investigator (Smithwick)¹³ who combined the two procedures developed a technic consisting of removal of the 12th rib, division of the diaphragm and removal of the splanchnic nerves from the midthoracic region to the celiac ganglion and the sympathetic trunk from the 9th thoracic nerve to the 2nd lumbar ganglion. This operation was attended with a little higher fatality rate (2.8 per cent), but seemed to procure greater denervation than the others and to produce a more lasting postural hypotension. In a high percentage of cases this operation was followed by a lowering of both the diastolic and systolic blood pressures. This approach has been extended to include resection of other ribs and removal of the splanchnic nerves and sympathetic ganglia from the 1st thoracic nerve to the 5th lumbar ganglion in one series,¹⁶ from the 3rd thoracic nerve to the 2nd lumbar ganglion in a second series,¹⁴ and from the 7th thoracic to the 2nd lumbar ganglion in a third series.¹⁷

Thus, have developed the different types of operation for denervation of the so-called splanchnic vascular bed and the vessels of the lower extremities. There is no doubt that the more extensive types of denervation¹⁴⁻¹⁶ have their advantages, but there are also disadvantages. It has been proved, both experimentally and clinically, that too extensive resection of the sympathetic nervous system is followed by changes in certain functions subservient to these nerves. After the performance of quadrilateral sympathectomy for the relief of vascular disease such as thrombo-angiitis obliterans and Raynaud's disease, there is an absence of sweating in all extremities, so that the burden of bodily sweating is placed on the unaffected area. This is true in the case of performance of more extensive resection of the thoracic and lumbar sympathetic ganglia and, even though the response relating to the hypertension may be superior, the comfort of the patient must be considered, especially those patients who live in a warm climate or even those who live in a changing climate. Excessive sweating of any part of the body can be disabling and incapacitating, as evidenced by patients suffering from hyperhidrosis.

COMMENT

The surgical treatment for the relief of hypertension has passed through the stage of radical rhizotomy into that of extraspinal resection of the splanchnic nerves and the thoracic and lumbar sympathetic ganglia and trunks.

Classification and grouping of the disease have been chosen arbitrarily for a comparison between the medical treatment, on the one hand, and various types of surgical procedures, on the other. No satisfactory single criterion for the prediction of successful operations has been developed. It has been agreed that even the most extensive of the operations cannot change the clinical status of hypertension which has advanced to the degree of irreversible changes in the vessels of the heart, kidneys, brain and other organs.

The nature of the operation is physiologic rather than pathologic and the results depend on the physiologic response of the vascular system. All types of sympathectomy and splanchnicectomy have been followed by arrest of the progress of the disease and alleviation of symptoms. Although it is true that the more extensive operations have resulted in greater denervation of the

vascular system, they also result in a more extensive cutaneous area of non-sweating which produces discomfort to the patient in adjusting to climatic changes, and further discomfort is experienced because of excessive sweating in the unaffected areas.

White¹⁸ has aptly summed up the present status of the surgical treatment of hypertension as follows: "Although it is not yet established that the results will be permanent, at least there is good reason to believe that the hands of the clock can be set back for a number of years in the majority of younger patients with hypertension who have not been permitted to progress to the stages of advanced degeneration or changes in heart, kidney or brain."

TABLE I
VARIOUS TYPES OF SURGICAL OPERATIONS FOR HYPERTENSION

- I. Rhizotomy:
 - a. Intraspinal division of anterior or motor roots of 6th thoracic nerve to 2nd lumbar nerve.⁴
 - b. Intraspinal division of anterior or motor roots of 9th thoracic nerve to 2nd lumbar nerve.⁹
- II. Sympathectomy and splanchnicectomy:
 - a. Subdiaphragmatic, 1st and 2nd lumbar sympathetic ganglia.^{10,11}
 - b. Supradiaphragmatic, 10th, 11th and 12th thoracic sympathetic ganglia.¹²
 - c. Transdiaphragmatic, 9th thoracic nerve to 2nd lumbar ganglion.¹³
 - d. Transdiaphragmatic, 3rd thoracic nerve to 2nd lumbar ganglion.¹⁴
 - e. Combined subdiaphragmatic and supradiaphragmatic:
 1. 1st thoracic nerve to 4th and 5th lumbar ganglia.^{15,16}
 2. 7th thoracic nerve to 2nd lumbar ganglion.¹⁷

REFERENCES

- ¹ Grimson, K. S.: The Surgical Treatment of Hypertension: Collective Review. *Internat. Abstr. Surg.*, 75, 421-434, November, 1942.
- ² Ayman, David: Heredity in Arteriolar (Essential) Hypertension: A Clinical Study of the Blood Pressures of 1,524 Members of 277 Families. *Arch. Int. Med.*, 53, 792-802, May, 1934.
- ³ Hines, E. A., Jr., and Brown, G. E.: The Hereditary Factor in the Reaction of Blood Pressure to a Standard Stimulus (Cold): Preliminary Report. *Proc. Staff. Meet., Mayo Clin.*, 10, 371-373, June 12, 1935.
- ⁴ Keith, N. M.: II. Cardiovascular Diseases in Relation to the Retina. *Tr. Am. Acad. Ophth.*, 37, 37-49, 1932.
- ⁵ Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease, with Hypertension and the Associated Retinal Lesions. *Medicine*, 18, 317-430, September, 1939.
- ⁶ Keith, N. M., Wagener, H. P., and Barker, N. W.: The Problem of Prognosis in Essential Hypertension: A Follow-up Study in 219 Cases. *Tr. A. Am. Physicians*, 53, 81-87, 1938.
- ⁷ Grimson, K. S., Kernodle, C. E., Jr., and Hill, H. C.: Hypertension: The Effect of Activity, Rest, Natural Sleep, Sodium Amytal, Pentothal Sodium, Chloralose and Ether on Experimental Neurogenic Hypertension and of Rest and Sodium Amytal and Anesthesia on Hypertensive Patients. *J. A. M. A.*, 126, 218-221, September 23, 1944.
- ⁸ Adson, A. W., and Brown, G. E.: Malignant Hypertension: Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots from the 6th Thoracic to the 2nd Lumbar, Inclusive. *J. A. M. A.*, 102, 1115-1118, April 7, 1934.
- ⁹ Brown, G. E., Craig, W. McK. and Adson, A. W.: The Treatment of Severe Essential Hypertension; Effects of Surgical Procedures Applied to the Sympathetic Nervous System. *Minnesota Med.*, 18, 134-138, March, 1935.
- ¹⁰ Adson, A. W.: Essential Hypertension: A Report of the Results Obtained by Bilateral Ventral Rhizotomy (6th Thoracic to 2d Lumbar Roots) and Bilateral Resection of Splanchnic Nerves. *J. Nerv. & Ment. Dis.*, 82, 190-193, August, 1935.

- ¹¹ Adson, A. W., Craig, W. McK. and Brown, G. E.: Surgery in Its Relation to Hypertension. Surg., Gynec. & Obst., 62, 314-331, February, 1936.
- ¹² Peet, M. M.: Splanchnic Resection for Hypertension; A Preliminary Report. Univ. Hosp. Bull., Ann Arbor, 1, 17-18, June, 1935.
- ¹³ Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension; Preliminary Report. Surgery, 7, 1-8, January, 1940.
- ¹⁴ Hinton, J. W., and Lord, J. W., Jr.: Operative Technique of Thoracolumbar Sympathectomy. Surg., Gynec. & Obst., 83, 643-646, November, 1946.
- ¹⁵ Grimson, K. S.: The Sympathetic Nervous System in Neurogenic and Renal Hypertension; Experimental Correlation and Clinical Consideration. Arch. Surg., 43, 284-305, August, 1941.
- ¹⁶ Grimson, K. S.: Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in Treatment of Hypertension. Ann. Surg., 114, 753-775, October, 1941.
- ¹⁷ Poppen, J. L.: Technic for Supradiaphragmatic and Infradiaphragmatic Sympathectomy for Hypertension. Lahey Clin. Bull., 3, 151-158 (July) 1943; Correction in 3, 187, October, 1943.
- ¹⁸ White, J. C.: Progress in Surgery of the Autonomic Nervous System, 1940-1942. Surgery, 15, 491-517, March, 1944.

Mayo Clinic
Rochester, Minn.

DISCUSSION.—DR. FRANK H. LAHEY, Boston, Mass.: I wish to disclaim any experience with operations for hypertension, but as I said to Doctor Craig, one of the most important things a clinic such as ours can do is to report our end-results as often as possible in these cases in order that we may determine what to expect from them. It is essential that the end-results of the various operations for hypertension be put on record as soon as possible, and in as significant numbers as possible.

These are the results in 100 consecutive cases in which operation was carried out in the neurosurgical department by Dr. James L. Poppen and the patients' course followed from one and one-half to four years. These results are being reported by Doctor Poppen in a paper sent to the Journal of the American Medical Association. All these patients have had one type of operation, a technic devised by Doctor Poppen in which he removes the thoracic and lumbar sympathetic chain in continuity from the fourth dorsal to the second lumbar ganglia, inclusive. This is accomplished by the removal of a small segment of the medial portion of the 11th rib and also the 7th or 8th rib depending on the amount of lordosis of the thoracic spine. A paper on the technic employed is in press. Doctor Poppen has tried to divide these results into "good," "fair" and "unsatisfactory." A good result is to be expected when, after operation, the maximum blood pressure is 150 mm. systolic and 100 mm. diastolic, the patient is in good physical condition and relieved of all symptoms associated with hypertension. Doctor Poppen has found, as Doctor Craig has, that there is no test by which one can predict in which case there will be a good result, and I am sure that everyone is anxious to get some test to determine that. It is not possible to select these cases by the blood pressure alone. They have determined not only the blood pressure in the cases in which the results are classified as fair, poor and unsatisfactory but have included, also, the reversal of electrocardiographic findings, roentgenologic evidence of change in the size of the heart and improvement in the arterioles of the retina and subjective symptoms. These they have placed last, as of the least significance.

In these cases the results have been good in 47 per cent, fair in 24 per cent and unsatisfactory in 22 per cent. The mortality has been 0.5 per cent. It is interesting in interpreting these findings that there has been a drop in blood pressure in 71 per cent, but in some of these there have not been associated satisfactory changes of the character I spoke of (such as the roentgenogram of the heart and the electrocardiogram, *etc.*) and so they have not been included in the satisfactory group.

Doctor Poppen in the follow-up of his group of cases has ascertained the effect of this operation upon sexual power. This is one of the important things we have to tell male patients before operating upon them by this plan. We all know the relationship of the lumbar ganglia and their influence upon the ejaculation power and it has been of interest to know what the effect has been. Fifty-eight per cent of this group were females, 42 per cent were males. Of these latter, 41 per cent had normal ejaculation after operation and 21 had no ejaculation, and in 18 per cent the power of ejaculation was diminished. It is also important to note what the effect has been on libido or potency, and Doctor Poppen reports that it is the same in 65 per cent, diminished in 23 per cent, and here is a strange fact concerning the question of the complete control of the power of ejaculation by the 1st or 2nd lumbar ganglion—libido and potency were improved in 12 per cent. In women there has been no change, and there have been pregnancies in some of the cases.

Since this is a group of patients operated upon by the same individual by the same technical plan and followed from one and one-half to four years, we thought it would be valuable to present them in relation to Doctor Craig's paper.

DR. LOYAL DAVIS, Chicago: In 1939, Dr. Marion H. Barker and I presented before this Association our experiences with the surgical treatment of patients with hypertension, by removal of portions of the sympathetic nervous system. Deliberately, we confined ourselves to a study of those patients who had been treated by various medical measures without success, but, in particular, all the patients had been resistant to the administration of potassium sulfocyanate.

This group of patients had been under observation for from seven to ten years, and we are now engaged in compiling an accurate and meticulous survey of their present condition. Many of them are enjoying a satisfactory social and economic existence on the cyanate regimen who, without operation and the resulting sensitivity to cyanates, we believe would have succumbed to their disease. Our experience with cyanate therapy and with sympathectomy in cyanate-resistant patients has been supported by the findings in other clinics.

It is obvious that many, in fact, the majority of the patients with essential hypertension whom we see in the clinic, belong to the group who react satisfactorily to the cyanates when they are properly administered and controlled. We have not as yet subjected this group to operation, but it is our opinion that were we to do so, the results following sympathectomy alone would be comparable to those reported from other clinics. In fact, after using all the proposed preoperative tests to determine whether or not sympathectomy may benefit the patient, we have come to believe that the therapeutic test with the cyanates is the most reliable. In addition to our own patients, our experience with patients operated upon elsewhere who come under Doctor Barker's management, supports this tentative conclusion.

The cyanate-resistant patient with hypertension belongs to the most unpredictable group whose course may suddenly become fatal, but for the same reason they constitute the group for whom every possible therapeutic measure should be employed. By limiting our own investigations to a single group of clinically well-defined patients, we believe that the final evaluation of the surgical treatment of hypertension will be materially hastened, and we are hopeful that our clinics will add to our experiences with this group of patients.

DR. WINCHELL MCK. CRAIG, Rochester, Minn. (closing): I am extremely grateful for this discussion. As I stated, I was trying to bring out the problems of surgical treatment of hypertension. The remarks of Doctor Lahey and Doctor Davis have shown that we have kept in mind the effect on patients and, following the statement of Doctor Davis, we hope, in connection with laboratory studies and further pharmaceutical studies, to further the treatment of hypertension.

CHRONIC SHOCK: THE PROBLEM OF REDUCED BLOOD VOLUME IN THE CHRONICALLY ILL PATIENT*

PART I—CONCEPT OF CHRONIC SHOCK

JOHN H. CLARK, M.D.,** WOODROW NELSON, M.D.,
CHAMP LYONS, M.D., H. S. MAYERSON, PH.D.,
AND
PAUL DeCAMP, M.D.,
NEW ORLEANS, LA.

FROM THE DEPARTMENTS OF PHYSIOLOGY AND SURGERY, TULANE UNIVERSITY, SCHOOL OF MEDICINE,
AND THE RESEARCH LABORATORIES OF THE ALTON OCHSNER MEDICAL FOUNDATION, NEW ORLEANS, LA.

A REDUCED TOTAL QUANTITY of circulating blood in patients with nutritional deficiency was reported by Chang¹ in 1932. Similar observations in hypoproteinemic animals have been recorded in the reports of the experiments of Holman, Mahoney and Whipple,² and of Elman and Davey.³ In a study of patients with persistently unhealed war wounds, attention was directed to a syndrome characterized by weight loss, reduced blood volume and increased interstitial fluid volume.⁶ Diminished blood volume in debilitated patients has also been noted by Gregersen,⁴ and by Varco.⁵ All these reports emphasize the coincidence of protein depletion and diminished blood volume. The surgically significant feature of reduced blood volume is an increased susceptibility to shock correctable by transfusion replacement of the blood volume deficit.⁶ It is on this basis that it is proposed to designate the syndrome as "chronic shock."

Much of an admittedly controversial nature precludes immediate acceptance of this concept of a reduced blood volume attributable to depletion of body protein. On the other hand, it has been possible to integrate such a mechanism in orderly relationship to currently accepted physiologic processes. Four years' experience with the clinical application of this hypothesis has offered considerable proof of the fundamental integrity of the underlying teleologic deductions. It is the purpose of this series of papers to present the rationale and factual data upon which the syndrome of "chronic shock" has been postulated.

Starling⁷ described the mechanism whereby the hydrostatic force of the capillary blood pressure and colloid osmotic pressure of the plasma proteins effected an interchange of fluid across the semipermeable capillary wall. Schade,⁸ in an extension of Landerer's⁹ earlier concepts, added the factor of tissue tension as contributory to the return of fluid from the interstitial reser-

* This is the first report of a series of studies being conducted under a grant from the Research and Development Division, Office of the Surgeon-General, United States Army.

** Doctor Clark's present location is Salt Lake City, Utah.

Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

voir to the vascular compartment. Tissue tension was accepted by Peters,¹⁰ and emphasized by Youmans,¹¹ as the only available mechanical force to supply a necessary increment of pressure. It is now recognized that some protein leakage across the capillary wall occurs normally.¹² The effective filtration forces of capillary blood pressure (BP), osmotic pressure of plasma protein (PP), tissue tension, or pressure (TE) and osmotic pressure of interstitial fluid protein (IFP) are diagrammatically summarized in Figure 1.

The usual distribution of the extracellular fluid is such as to maintain a ratio of plasma volume to interstitial fluid volume of 1:3.¹³ However, wide variation in the total quantity and apparent distribution of the extracellular fluid is known to occur.¹⁴⁻¹⁷ It has been concluded that these fluctuations maintain plasma volume through a reciprocal balance of the filtration forces mediated by the osmotic pressure of the plasma proteins and the tissue tension respectively.^{14, 16} This relationship is presented schematically in Figures 2, 3 and 4.

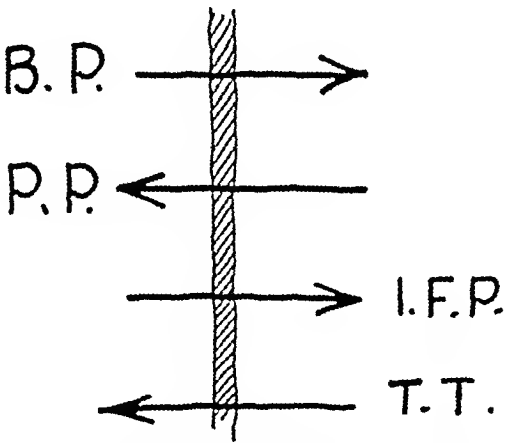


FIG. 1.—Diagrammatic representation of filtration forces across the capillary wall.

B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; I. F. P., osmotic pressure of interstitial fluid protein; T. T., tissue tension or pressure.

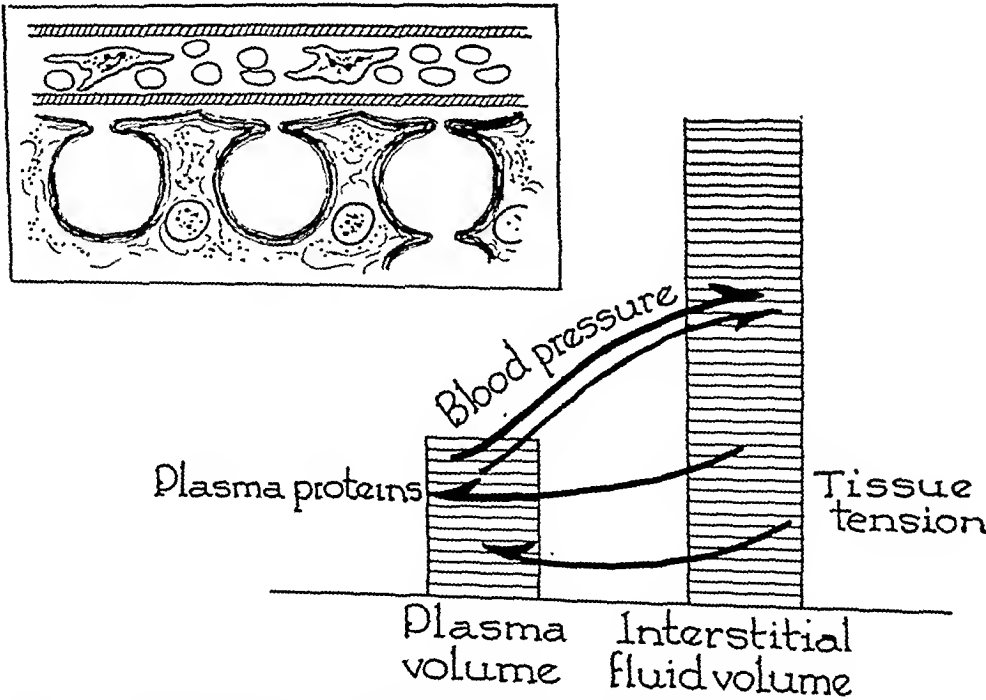


FIG. 2.—Diagrammatic representation of normal forces acting to maintain P. V.: I. F. V. ratio.

Failing of explanation within this concept are numerous clinical observations of increased interstitial fluid volume and decreased plasma volume, with

normal concentration of plasma proteins.^{4, 6, 15} In dogs maintained on a protein-inadequate diet or rendered edematous by plasmapheresis, edema has been noted in the absence of significant lowering of the concentration of plasma proteins.¹⁸ The persistence of a normal pattern of plasma protein concentration has been confirmed by Tiselius determinations upon the plasma

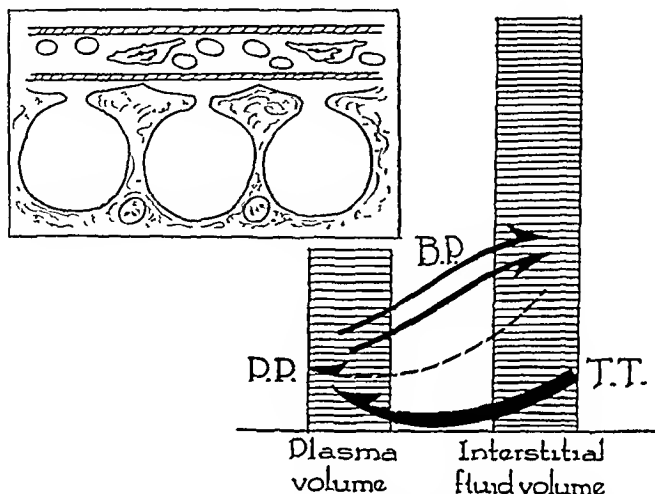


FIG. 3.—Diagrammatic representation of forces acting to maintain P. V. : I F. V. ratio in sodium retention and hydremia

B. P., capillary blood pressure, P. P., osmotic pressure of plasma protein; T. T., tissue tension or pressure.

TABLE I

PLASMA VOLUME—INTERSTITIAL FLUID VOLUME RATIO IN PATIENTS WITH DELAYED WOUND HEALING*

Patient	Weight Loss (Kg)	Conc of Plasma Prot (Grams %)	Plasma Volume (Ml)	Interstitial Fluid Volume (Ml)	Ratio P.V : I F.V.
1	0		3,900	13,900	1 : 3.3
2	4.2	8.0	2,900	15,900	1 : 5.4
3	5.6		2,400	13,500	1 : 5.6
4	6.4	6.9	3,200	13,800	1 : 4.3
5	14.4	8.0	2,400	12,100	1 : 5
6	14.9	7.6	2,600	15,800	1 : 6
7	15.1		2,100	15,100	1 : 7.1
8	16.7	6.7	2,600	16,600	1 : 6.4
9	30.0	7.2	2,700	15,800	1 : 5.8

* The analyses were made by Miss Margaret Rourke by concomitant determinations of the plasma volume with the dye T-1824²⁰ and extracellular fluid volume with sodium thiocyanate²¹. Plasma proteins were determined by Kjeldahl analysis.

of human subjects with edema¹⁹ due to famine. Certain unpublished observations from a previous study⁶ are pertinent in this regard. The clinical subjects were soldiers depleted in consequence of prolonged exudation from persistently open war wounds. The findings are summarized in Table I. Alteration of the usual 1 : 3 ratio of plasma volume to interstitial fluid volume is the consequence of decrease in the plasma volume and increase of the interstitial

fluid volume. There is no real correlation between the amount of weight lost and the degree of alteration of the ratio, comparable changes being noted with a loss of nine pounds (Patient No. 2), and 65 pounds (Patient No. 9). As previously noted,⁶ there is correlation of reduced body weight, reduced plasma volume and reduced total mass of circulating blood proteins, both hemoglobin and plasma protein.

Schoenheimer's²² concept of the dynamic equilibrium of all the body proteins warrants the conclusion that protein depletion should affect tissue protein as well as blood proteins. It has now been shown that weight loss is correlated with reduced total mass of blood proteins even though the concentration of the blood proteins is not significantly altered. Masked deficiencies of this sort

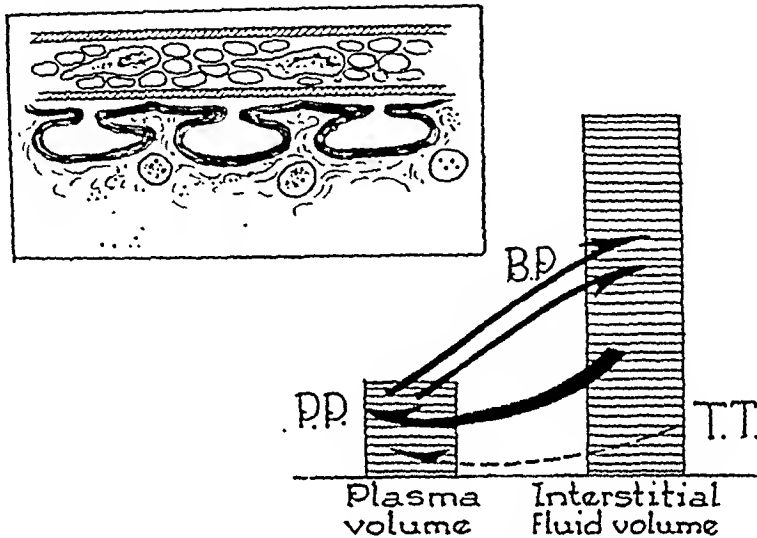


FIG. 4.—Diagrammatic representation of forces acting to maintain P. V.:I. F. V. ratio in dehydration and oligemia.

B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; T. T., tissue tension or pressure.

have been recognized previously.²³ Recognition of the factor of tissue protein depletion offers a mechanism whereby the interstitial fluid volume could expand as the result of reduced tissue tension associated with loss of some tissue protein, such as collagen.¹⁸ Loss of tissue tension implies that the quantity of the plasma volume is predetermined by the *hygroscopically active concentration* of a reduced total mass of plasma colloids. Such an explanation fits the factual data rather well. This postulated mechanism is presented in Figure 5. Other students of this problem have emphasized alteration of the physiologic integrity of the capillary wall.¹⁹ Robertson and Bock²³ found it impossible to restore blood volume beyond a certain point when further increase in plasma volume would, by dilution, have reduced the hemoglobin concentration percentage to a very low figure. Anemia, in consequence of reduced total mass of hemoglobin, has been shown to favor loss of fluid and protein from the vascular to the interstitial fluid compartment.²⁴

The exact mechanism whereby the recorded changes are produced is admittedly complex. Important for clinical emphasis is the observation that

in patients with weight loss the reduced plasma volume may mask deficiencies in the total mass of blood proteins. The significance of increased interstitial fluid volume remains to be elucidated.

DISCUSSION.—The concept of a state of "chronic shock" may be protested on several grounds. Gregersen, and others,^{4, 25, 26} have answered most of the theoretic and technical dissatisfactions with the method of blood volume determination. Criticism based on the known variation in the plasma volume among "normal" subjects²⁷ has been countered by consideration of the plasma volume

TABLE II
CONSTANCY OF THE PLASMA VOLUME IN NORMAL INDIVIDUALS

Date 1946	Subject			
	W. W.	W. N.	H. M.	R. K.
January.....	2,625		2,535	
February.....		3,515	2,750	
March.....			2,795	
April.....		3,335		
May.....	2,730			
June.....				3,130
July.....				
August.....	2,690			3,350

TABLE III
CHANGES IN WEIGHT AND BLOOD VOLUME DURING CONVALESCENCE

Date	Weight	Blood Volume
4/2/46.....	106 lbs.	3,400 MI.
5/9/46.....	83 lbs.	4,400 MI.
6/20/46.....	85 lbs.	4,600 MI.

Patient entered with carcinoma of stomach resected on 4/26/46. No postoperative transfusions were given. Weight prior to illness was 128 pounds. It should be noted that blood volume restoration and maintenance during convalescence reveals a deficiency of 1,200 MI. at the time of the initial blood volume determination.

to interstitial fluid volume ratio and by serial determinations of the blood volume in individual patients. Hematologists²⁸ are reluctant to accept a concept invalidating the hemoglobin concentration as an accurate index of the total quantity of circulating hemoglobin, although biochemists have long emphasized the fallacy of assuming that solute concentrations reflect the plasma volume.²⁹⁻³¹

The constancy of the plasma volume, as demonstrated by serial determinations in a series of given individuals, is attested in Table II. The presence of reduced blood volume in a patient with weight loss is confirmed by the demonstration of restoration of blood volume to a higher level during convalescence (Table III). It has been repeatedly observed that restoration of the blood volume precedes significant recovery of weight during recuperation from debilitating illness. Methods of evaluating the blood volume deficit in

CHRONIC SHOCK

patients with weight loss and the quantitative aspects of transfusion restoration of blood volume will be reported subsequently.

Clinical practice in the restoration of structural defects of the extracellular fluid has been based on Gamble's¹³ demonstration of the ability of the normal kidney to retain selectively the needed electrolyte. Quite recently, Coller, and coworkers,³² challenged this established program by presenting evidence of excessive retention of water, sodium and chloride in patients with sound kidneys and normal concentrations of the plasma proteins. The subjects of

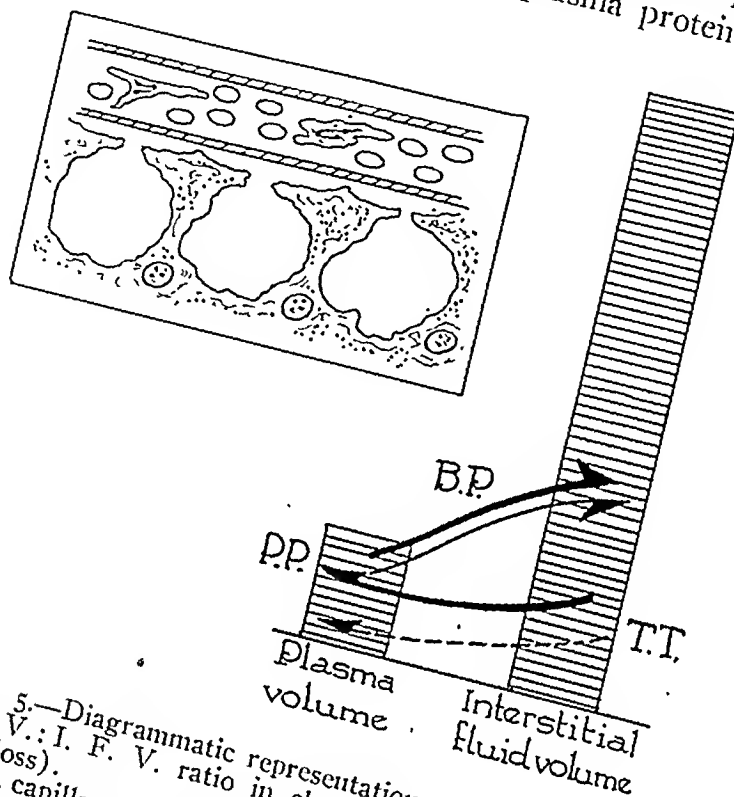


FIG. 5.—Diagrammatic representation of forces affecting P. V.: I. F. V. ratio in chronic sepsis (anemia of weight loss).
B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; T. T., tissue tension or pressure.

the study were patients with neoplastic lesions of the rectosigmoid colon, but no data as to weight loss were provided in the clinical protocols. However, the unexpected findings of Coller's group are readily explained within the postulated syndrome of "chronic shock." A similar translocation of intravenously administered fluid was recorded in consequence of depletion of the total circulating hemoglobin and in patients with chronic sepsis by Robertson and Bock.²³ Comparable and unexplained shifts of the extracellular fluid were recorded in consequence of surgical operation and ether anesthesia by Stewart and Rourke.¹⁵

In spite of the many uncertainties, the fact remains that there is much of clinical utility in these considerations. The clinical appraisal of weight loss in terms of protein depletion and reduced blood volume has led to more accurate evaluation of the "poor risk" patient than measurements of the concentration

of hemoglobin and plasma protein alone. Correction of blood volume deficits by blood transfusions has proved to be the most important single factor in the preparation of such patients for surgical treatment and subsequently effective utilization of ingested protein. The concept of "chronic shock" is at least temporarily useful in the routine management of debilitated patients, in the comprehension of apparently conflicting clinical studies and in the formulation of new investigative programs of clinically pertinent problems.

CONCLUSIONS

1. Weight loss, decreased blood volume, decreased blood proteins and increased interstitial fluid volume have been correlated as the surgically significant features of protein depletion of the body in a syndrome of "chronic shock."

2. Body protein has been presented as a factor in the dynamic equilibrium of fluid exchange across the capillary wall.

3. The necessity for adoption of some modification of current concepts has been indicated.

REFERENCES

- ¹ Chang, H. C.: Plasma Protein and Blood Volume. *Proc. Soc. Exper. Biol. & Med.*, **29**, 829-832, 1932.
- ² Holman, R. L., Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet; Liver and Casein as Potent Diet Factors. *J. Exper. Med.*, **59**, 251-267, 1934.
- ³ Elman, Robert, and Davey, H. W.: Studies on Hypoalbuminemia Produced by Protein-deficient Diets: The Correction of Hypoalbuminemia in Dogs by Means of Large Plasma Transfusions. *J. Exper. Med.*, **77**, 1-5, January, 1943.
- ⁴ Gregersen, M. I.: A Practical Method for the Determination of Blood Volume with the Dye T-1824. *J. Lab. & Clin. Med.*, **29**, 1266-1286, December, 1944.
- ⁵ Varco, R. L.: Preoperative Dietary Management for Surgical Patients: With Special Reference to Lesions of the Stomach and Duodenum. *Surgery*, **19**, 303-378, 1946.
- ⁶ Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army: A Report. *J. A. M. A.*, **123**, 1007-1018, December 18, 1943. ✓
- ⁷ Starling, E. H.: *The Fluids of the Body*. London, Constable and Co., Ltd. 1909.
- ⁸ Schade, H.: Über Quellungsphysiologie und Ödementstehung, *Ergebn. d. inn. Med. u. Kinderh.*, **32**, 425-463, 1927.
- ⁹ Landerer, A. S.: *Die Gewebsspannung in ihrem Einfluss auf die oertliche Blut- und Lymphbewegung*, Leipzig, 1884.
- ¹⁰ Peters, J. P.: *Body Water. The Exchange of Fluid in Man*. Springfield, Charles C. Thomas, 1935.
- ¹¹ Youmans, J. B., Wells, H. S., Donley, D., and Miller, D. G.: Effect of Posture (Standing) on Serum Protein Concentration and Colloid Osmotic Pressure of Blood from Foot in Relation to Formation of Edema. *J. Clin. Investigation*, **13**, 447-459, 1934.
- ¹² Fulton, J. F.: *Howell's Textbook of Physiology*, Philadelphia. W. B. Saunders Co., 1946.
- ¹³ Gamble, J. L.: *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, (a Lecture Syllabus)*, Harvard Medical School, Boston, Spaulding-Moss, 1941.
- ¹⁴ Warren, J. V., Merrill, A. J., and Stead, E. A., Jr.: *The Role of Extracellular Fluid*

- in the Maintenance of a Normal Plasma Volume. *J. Clin. Investigation*, 22, 635-641, September, 1943.
- 15 Stewart, J. D., and Rourke, M.: Changes in Blood Volume and Interstitial Fluid Resulting from Surgical Operations and Ether Anesthesia. *J. Clin. Investigation*, 17, 413-416, July, 1938.
 - 16 Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure. *Arch. Int. Med.*, 73, 138-147, February, 1944.
 - 17 Gibson, J. G., Jr., and Kopp, I.: Studies in the Physiology of Artificial Fever: I—Changes in the Blood Volume and Water Balance. *J. Clin. Investigation*, 17, 219-232, May, 1938.
 - 18 Weech, A. A., Snelling, C. E., and Goettsch, E.: The Relation between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein-Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis. *J. Clin. Investigation*, 12, 193-216, 1933.
 - 19 Keys, A., Taylor, H. L., Mickelsen, O., and Henschel, A.: Famine Edema and the Mechanism of Its Formation. *Science*, 103, 669-670, May 31, 1946.
 - 20 Gregersen, M. I., Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; the Use of the Blue Dye T-1824. *Am. J. Physiol.*, 113, 54-5, September, 1935.
 - 21 Crandall, L. A., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate. *Am. J. Digest. Dis.*, 1, 126-131, April, 1934.
 - 22 Schoenheimer, R.: *The Dynamic State of Body Constituents*. Cambridge, Mass., Harvard University Press, 1942.
 - 23 Robertson, O. H., and Bock, A. V.: Blood Volume in Wounded Soldiers. *J. Exper. Med.*, 29, 139-172, February, 1919.
 - 24 Landis, E. M.: Micro-injection Studies of Capillary Permeability: III. The Effect of Oxygen Lack on the Permeability of the Capillary Wall to Fluid and to Plasma Proteins. *Am. J. Physiol.*, 83, 528-542, January, 1928.
 - 25 Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo dye "Evans Blue" and the Spectrophotometer. *J. Clin. Investigation*, 16, 301-316, May, 1937; II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in 90 Normal Humans. *J. Clin. Investigation*, 16, 317-328, May, 1937.
 - 26 Cruickshank, E. W. H., and Whitfield, I. C.: The Behavior of T-1824 (Evans Blue) in Circulating Blood and a Modified Method for the Estimation of Plasma Volume. *J. Physiol.*, 104, 52-59, 1945.
 - 27 Griffin, G. E., Abbott, W. E., Pride, M. P., Muntwyler, E., Mantz, F. R., and Griffith, L.: Plasma Volume, "Available (Thiocyanate) Volume" and Total Circulating Plasma Protein in Normal Adults. *ANNALS OF SURGERY*, 121, 352-360, March, 1945.
 - 28 Cartwright, G. E., Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia and Alterations in Porphyrin Metabolism in Patients. *J. Clin. Investigation*, 25, 65-80, January, 1946.
 - 29 Marriott, W. McK.: Anhydremia. *Physiol. Rev.*, 3, 275-294, April, 1923.
 - 30 Peters, J. P., Wakeman, A. M., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition. *J. Clin. Investigation*, 3, 491-495, February, 1927.
 - 31 McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction. *J. A. M. A.*, 91, 1589-1592, November 24, 1928.
 - 32 Coller, F. A., Iob, V., Vaughan, H. H., Kalder, N. B., and Moyer, C. A.: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively. *ANNALS OF SURGERY*, 122, 663-677, October, 1945.

(Continue with Part II)

PART II—HEMOGLOBIN AND RED BLOOD CELL DEFICITS
IN CHRONIC SHOCK*

There is good reason to believe that a deficiency of hemoglobin is a factor of primary importance in the problems engendered by depletion of body proteins. Certainly, the wounds of the anemic patient heal slowly and convalescence is generally retarded. A more succinct expression of this general clinical principle has been provided in the experimental work of Whipple, and his coworkers. In the presence of a deficiency of both hemoglobin and tissue protein, priority is assigned to the fabrication of new hemoglobin.^{1, 2} It appears that restoration of protein deficits may be expedited by initial correction of anemia.

There is a definite ceiling on the rate of synthesis of new hemoglobin.^{3, 4} The time required for red blood cell and hemoglobin regeneration may fail to meet the surgical exigency in a chronically ill patient. In many cases operation cannot be wisely postponed until the patient has synthesized adequate quantities of both hemoglobin and tissue protein. Tissue protein regeneration, in the absence of anemia, is accomplished rapidly.⁵ Thus, immediate correction of anemia by whole blood transfusion theoretically assures the deviation of newly available protein to the more rapidly accomplished synthesis of tissue and plasma proteins.

In chronically ill patients the anemia may be so masked by reduction in plasma volume that the hematocrit concentration fails to give a true picture of the existing deficiencies in hemoglobin and red blood cells. Initial observations of surgically significant reductions in blood volume associated with weight loss were made in soldiers with persistently unhealed and suppurative wounds.⁶ Diminished blood volume in debilitated patients has also been noted by Gregersen,⁷ and Varco.⁸ To designate the syndrome characterized by protein depletion, diminished blood volume, and increased susceptibility to shock correctable by transfusion replacement of the blood volume deficit, we⁹ have recently introduced the term, "chronic shock." It is the purpose of this paper to consider the quantitative aspects of the red blood cell and hemoglobin deficits in chronic shock and the correction of these deficits by whole blood replacement.

PROCEDURE AND METHODS

Initial determinations of body weight, plasma volume, hematocrit, hemoglobin concentration and plasma specific gravity were made in 89 patients with a clinical history of weight loss. Included were 41 patients with malignant disease, 28 with chronic infection, eight with hepatic disease, seven with malnutrition and five with peptic ulceration. Among the 89 patients, serially

* This is the second report of a series of studies being conducted under a grant from the Research and Development Division, Office of the Surgeon-General, United States Army.

repeated determinations were made on 59 patients. Sixteen normal subjects with repeated observations on nine served as a control group.

The volume changes in response to transfusion therapy were observed in 33 patients. In most, indicated surgical procedures were performed during the period of hospitalization and initial study. Insofar as possible, blood lost during operation was replaced. Subsequent observations during convalescence were made on an ambulatory program through out-patient facilities. Especial attention was given to a high dietary intake of protein, supplemented when necessary by oral or jejunal feedings of protein digests or hydrolysates.

Considerable care was devoted to standardization of the procedures used. All patients were studied under basal conditions. Breakfast was omitted, and the patients rested quietly in the recumbent position for at least ten minutes before the determinations were made. Blood was drawn from an antecubital vein into syringes coated with a thin film of heparin. Total circulating plasma volume was determined by the method of Gregersen,⁷ the Klett-Summerson photo-electric colorimeter being used. Red blood cell volumes were calculated from hematocrit values obtained with Wintrobe tubes. These tubes, as well as the samples used for obtaining plasma, were centrifuged for 30 minutes at 3,000 revolutions a minute. Hematocrit determinations were made on the samples of blood taken before and after injection of the dye. This served as a check on possible shifts during the ten-minute intervening period. Hemoglobin was determined as oxyhemoglobin by the photo-electric colorimetric method of Evelyn,¹⁰ and total circulating hemoglobin was calculated from the total blood volume value. Specific gravity of the plasma was determined by the falling-drop method of Barbour and Hamilton,¹¹ and plasma protein percentage by the formula of Weech, Reeves, and Goettsch.¹²

EXPERIMENTAL OBSERVATIONS

1. *Estimation of the Standard Circulating Blood Volume for Patients with Weight Loss.*—One of the most difficult problems in the clinical application of blood volume studies is evaluation of an isolated determination in a given patient. Various tables have been compiled to give standard or usual values on the basis of such factors as weight, height, age and sex. Rowntree, Brown and Roth,¹³ and Gibson and Evans,¹⁴ concluded that the blood volume bears a more constant relationship to body surface area than to weight, but their average values on the basis of weight were consistent in people of usual physical configuration. Average values for obese, tall and thin or elderly persons were predicted more accurately by correlation with body surface area. Gregersen, on the other hand, concluded that the correlation of blood volume with weight is as accurate as with body surface area. Particularly significant in this connection are the observations of Courtice¹⁵ on the identity of values based on weight for animals of such different surface areas as the rabbit, dog, goat and horse.

In Table I are presented the results of our determinations in 16 normal subjects as compared to the values reported by previous investigators.^{7, 14-19}

Our average value for plasma volume, 45.5 Ml./Kg., is practically identical with that reported by Gregersen,⁷ and Stewart and Warren,¹⁰ with the blue dye, T-1824. The average value for total blood volume, 82 Ml./Kg., is also similar to Gregersen's value of 85 Ml./Kg. Serial determinations in four

TABLE I
COMPARISON OF STANDARD VALUES

Determinations by:	Number of Cases	Method Dye Technic	Plasma Ml./Kg.	Blood Volume Ml./Kg.
Keith, Rowntree, and Geraghty, 1915.....	42	Vital Red	50	85
Bock, 1921.....	5	Vital Red	51	81
Rowntree, Brown, and Roth, 1929.....	78	Vital Red	53	88
Gibson and Evans, 1937.....	49 males 41 females	T-1824	43 males 42 females	78 66
Davis, 1942.....	11	T-1824	40.5	77
Gregersen, 1944.....	517	T-1824	45	85
Stewart and Warren, 1945.....	29	T-1824	45	..
Present series, 1946.....	16	T-1824	45.5	82

TABLE II
RELATIONSHIP OF BLOOD VALUES TO OBSERVED AND USUAL WEIGHT

Case No. and Diagnosis	Weight Observed and Usual	Total Hemoglobin	Total Cell Volume	Total Blood Volume
		Percentage of Standard for Weight*		
Case 306..... Carcinoma of stomach 83% of usual weight	Observed 48.1 Kg.	61	65	85
	Usual 58 Kg.	49	52	70
Case 301..... Carcinoma of colon 89% of usual weight	Observed 50.3 Kg.	69	67	100
	Usual 81.2 Kg.	41	41	60
Case 308..... Carcinoma of pancreas 62% of usual weight	Observed 43.5 Kg.	77	88	102
	Usual 69.8 Kg.	49	54	62
Case 403..... Achalasia 63% of usual weight	Observed 31.7 Kg.	81	93	131
	Usual 53.3 Kg.	54	58	84

* Standard values are taken from Gregersen.⁷

Total hemoglobin = 12.75 Gm./Kg.; total red cells = 40 Ml./Kg.; blood volume = 85 Ml./Kg.

normal subjects at varying intervals over a period of seven months showed a remarkable constancy, the range of variation being within 10 per cent.⁹

The data given in Table I suggest a close relationship between blood volume and body weight and indicate that standard values for the blood volume

of the normal individual can be safely calculated from observed weight. Table II indicates, however, that the problem is more complex when patients with progressive weight loss are involved. In transfusing such patients, one is confronted with the problem of selecting a standard on the basis of the optimal weight in health or on the basis of the observed weight in illness. Thus, in the four representative cases shown in Table II, it is seen that malnourished patients may have total hemoglobin, red cell and total blood volume values near

TABLE III
EFFECTS OF REPLACEMENT THERAPY

Case No., Diagnosis and Treatment	Determinations	Total Hemoglobin	Total Cell Volume	Blood Volume
		Percentage of Standard for Weight		
Case 306—64-year-old male..... Carcinoma of stomach Usual weight 128 lbs. (48.1 Kg.) Radical resection 4/26/'46 Procedure well tolerated Uneventful convalescence	4/10/'46			
	Weight 83% of usual	49	42	70
	4/26/'46—following replacement therapy with 3,000 Ml. Weight 78% of usual	100	115	106
	5/9/'46 3 weeks postoperative Weight 65% of usual	83	90	89
	6/20/'46 Postoperative Weight 66% of usual	89	93	94
Case 326—57-year-old male. Esophageal stricture Following esophagogastrctomy for malignancy (March, 1946) Usual weight 220 lbs. (99.8 Kg.) Gastrostomy 7/5/'46 Rapid clinical recovery following dilatation	7/1/'46			
	Weight 68% of usual	56	65	73
	7/5/'46—following replacement with 2,500 Ml. Weight unchanged	113	118	126
	7/17/'46 High protein gastrostomy feeding. Weight unchanged	90	90	78
	8/27/'46 Able to swallow high protein diet Weight 73% of usual	100	102	98

the assumed standard for their observed weight. Values calculated on the basis of their usual weight, however, are significantly lower. It may finally be pointed out that when blood volume for a patient with weight loss is computed on each of the three bases commonly used; that is, weight, surface area and height, better agreement is reached between the values based on weight and those obtained by the other methods if the normal, rather than the observed weight, is used. From inspection of the Dubois formula ($A = W^{0.425} \times H^{0.725} \times C$) for surface area it is seen, that a given loss in weight is accompanied by a smaller relative loss in surface area. Thus, a 25 per cent weight loss by

a 71-inch man who formerly weighed 186 lb. is attended by a 13 per cent decrease in surface area.

In similar patients one of us⁶ found it clinically practicable to restore the blood volume by transfusion to the standard value for the patient's usual weight without evidence of significant hemoconcentration or overloading of the vascular reservoir. The significance of this observation has been questioned on the basis of inadequate studies during convalescence to indicate maintenance of the blood volume at this higher level.²⁰ Table III shows the results of two typical experiments indicating that during convalescence after transfusion and appropriate surgical treatment the values for total circulating hemoglobin and total red blood cell mass are maintained at, or near, the standard value for the patient's usual weight in health. It is significant that restoration of

TABLE IV

STANDARD VALUES IN OBESE AND IN TALL AND THIN PATIENTS, AND IN PROTRACTED ILLNESS

Case No. and Diagnosis	Body Type	Weight Usual and Standard	Plasma Volume	Blood Volume
			Percentage of Standard	
Case 427..... Duodenal and esophageal ulceration (2,000 Ml. of blood prior to determinations)	Obese prior to illness	Usual weight 88.9 Kg.	82	72
		Standard for age, sex and height 68 Kg.	100	93
Case 520..... Bronchiectasis	Tall and thin	Usual weight 61.7 Kg.	104	99
		Standard for age, sex and height 79.4 Kg.	83	84
Case 518..... Bronchiectasis	Ill since childhood— never attained optimal weight	Usual weight 39.9 Kg.	100	89
		Standard for age, sex and height 50.8 Kg.	80	72

blood volume during convalescence precedes significant gain in weight. This is strikingly illustrated in Case 326 in which the transfusion of 2,500 Ml. of blood elevated the hemoglobin, red cell and blood volumes well above standard levels based on his usual weight. Following correction of an esophageal stricture and adequate dietary intake, these levels were maintained for six weeks with only a slight increase in weight.

We have found that in approximately 5 per cent of the cases the calculations of standard values on the basis of usual weight in health are not applicable. This is true in instances of excessive obesity prior to illness, in tall and thin patients and in protracted illness wherein optimal weight had never been attained. Our data (Table IV) suggest that in such cases it is preferable to use values based on standard weight tables for sex, age and height. It has not been found necessary to correct standards for the older age groups.

Further factual evidence supporting the use of standards based on usual weight in health is presented in Table V. Restoration of the blood volume

to the standard volume assigned on the basis of the usual weight in health may give values up to 150 per cent of normal for the observed weight. This has been accomplished without clinical or laboratory evidence of overloading of the vascular reservoir.

TABLE V
RESULTS OF TRANSFUSION THERAPY

Case No. and Diagnosis	Ml. of Blood Given	Hemato- crit %	Weight Observed and Usual	Total Hemoglobin	Total Cell Volume	Blood Volume
				Percentage of Standard		
Case 403..... Achalasia 63% of usual weight, 50.3 Kg.	1,500	40	Observed	120	123	144
			Usual	93	88	105
Case 327..... Carcinoma of lung 82% of usual weight, 61.7 Kg.	2,000	45	Observed	129	133	118
			Usual	113	119	105
Case 308..... Carcinoma of pancreas 62% of usual weight, 69.6 Kg.	2,000	49	Observed	102	114	110
			Usual	65	71	68
Case 322..... Carcinoma of lung 86% of usual weight, 103 Kg.	3,000	50	Observed	123	128	120
			Usual	103	108	103
Case 338..... Carcinoma of esophagus 83% of usual weight, 77 Kg.	2,350	52	Observed	124	132	120
			Usual	104	109	97
Case 306..... Carcinoma of stomach 83% of usual weight, 58 Kg.	3,000	53	Observed	127	135	136
			Usual	100	115	106
Case 332..... Carcinoma of pancreas 83% of usual weight, 74.8 Kg.	2,000	54	Observed	122	126	111
			Usual	101	107	91
Case 302..... Carcinoma of esophagus 87% of usual weight, 71.7 Kg.	3,500	54	Observed	122	133	119
			Usual	100	114	99
Case 334..... Carcinoma of lung 81% of usual weight, 68 Kg.	2,500	54	Observed	131	129	117
			Usual	108	110	96
Case 326..... Stricture of esophagus 89% of usual weight, 99.8 Kg.	2,500	55	Observed	168	175	150
			Usual	113	118	126

2. *Determination of Blood Volume in Patients with Weight Loss Due to Various Causes.*—Reduced blood volume was observed in all cases of weight loss investigated. In Table VI it is shown that average blood volumes for the various groups, expressed as per cent of standard for usual weight, were as follows: Malignancy, 72 per cent; chronic infection, 76 per cent; hepatic disease, 67 per cent; malnutrition, 76 per cent; and peptic ulceration, 79 per cent. The deficit is approximately one-fourth the value accepted as standard for the patient in health. The reduction in total hemoglobin and red cell mass

is more pronounced than that in total blood volume. The average total hemoglobin ranged from 50 to 66 per cent of the standard and the average total red blood cell mass ranged from 56-70 per cent of the standard. It is obvious that in this group of cases a clinical history of weight loss has consistently indicated reduction in blood volume and total circulating red cell mass.

3. *Total Circulating Hemoglobin and Total Red Cell Mass in Estimating Replacement Needs.*—Studies in World War II confirmed the existence of reduced blood volume in consequence of traumatic injuries.^{19, 21-25} In such

TABLE VI
TABULATION OF DEFICITS ASSOCIATED WITH WEIGHT LOSS

Disease	No. of Cases	Weight	Total Hemoglobin Per Cent of Standard	Total Cell Volume Per Cent of Standard for Usual Weight	Plasma Volume	Blood Volume
Malignancy.....	41	83	50	58	84	72
Chronic infection.....	28	87	59	59	92	76
Hepatic disease.....	8	84	52	56	84	67
Malnutrition.....	7	78	53	61	91	76
Peptic ulceration.....	5	85	66	70	88	79

TABLE VII
CORRELATION BETWEEN ANEMIA AND DIMINISHED PLASMA PROTEIN CONCENTRATION
IN TRAUMATIC INJURIES*

Hematocrit	Plasma Protein in G. %						Total Patients
	5.6-6	6.6-6.5	6.6-7	7.1-7.5	7.6-8	8.1-8.5	
20-30.....	2	9	4				15
31-40.....	2	6	14	14	3		39
41-50.....		6	8	19	4	1	38
Total patients...	4	21	26	33	7	1	92

* These observations were made in collaboration between Major Jos. E. Edwards and one of us (C. L.), by the CuSO_4 method, April, 1944.

injuries, there was correlation between anemia and plasma protein concentration (Table VII). Base Hospital surgeons, concerned with correction of anemia prior to reparative surgery and during early convalescence, evolved a rough "rule-of-thumb" to estimate transfusion requirements. It was recommended²⁶ that 500 Ml. of whole blood be given for each three-point deficit in the hematocrit. In practice, it was found safe to give 1,000 Ml. daily when the hematocrit was below 40 per cent, and 500 Ml. daily for a hematocrit of 40 to 45 per cent. In chronic shock, however, dosages based on hematocrit deficits are of little value because of the reduced plasma volume. The hematocrit concentration does not give a true picture of the existing deficiencies. Adequate restoration can be accomplished only by restoration of the total circulating hemoglobin or red cell mass, but the deficits cannot be determined accurately without blood volume studies.

As a result of our experience, certain general conclusions as to the amount of blood usually required may be drawn. The average hemoglobin deficit was 415 Gm. and the average deficit in red cell volume was 1,200 Ml. On the assumption that each 500 Ml. of transfused blood contains 75 Gm. of hemo-

globin and 225 Ml. of red blood cells, the average dosage of blood required was 2,700 Ml. In no instance has less than 1,500 Ml. been given and in some patients 4,000 Ml. has been necessary.

By definition, correction of anemia implies restoration of total hemoglobin to standard value. This has been attended by definite but asymptomatic

TABLE VIII
RESULTS OF REPLACEMENT THERAPY

RESULTS OF REPLACEMENT THERAPY

Case No. and Diagnosis	Transfusion Therapy*	Total Hemoglobin	Total Cell Volume
		Percentage of Standard	
(A) In absence of continued bleeding			
Case 335—Carcinoma of lung.	Prior to transfusion	65	72
Estimated transfusion dosage 1,800 Ml.			
Usual weight 79.8 Kg.	After transfusion with 2,000 Ml.	110	112
Case 334—Carcinoma of lung.	Prior to transfusion	58	63
Estimated transfusion dosage 2,300 Ml.			
Usual weight 68 Kg.	After transfusion with 2,500 Ml.	108	110
Case 509—Chronic empyema.	Prior to transfusion	56	57
Infection controlled with penicillin			
Estimated transfusion dosage 2,000 Ml.	After transfusion with 2,000 Ml.	103	115
Usual weight 47.6 Kg.			
Case 522—Bronchiectasis.	Prior to transfusion	67	66
Estimated transfusion dosage 1,650 Ml.			
Usual weight 61.2 Kg.	After transfusion with 1,500 Ml.	92	102
(B) In presence of continued bleeding			
Case 428—Large gastric ulcer.	Prior to transfusion	62	60
Estimated transfusion dosage 2,000 Ml.			
Usual weight 62.6 Kg.	After transfusion with 2,000 Ml.	65	64
Case 312—Large carcinoma of stomach. . .	Prior to transfusion	56	59
Estimated transfusion dosage 3,200 Ml.			
Usual weight 86 Kg.	After transfusion with 3,000 Ml.	80	81
Case 324—Carcinoma of head of pan- creas, with common duct obstruction	Prior to transfusion	66	73
Estimated transfusion dosage 2,000 Ml.			
Usual weight 70 Kg.	After transfusion with 3,350 Ml.	88	81

* The transfusion dosage was based on deficit in total grams of hemoglobin.

hemoconcentration. On the other hand, restoration of total circulating red cell volume has given clinically satisfactory results and more nearly normal hematocrit values.

No untoward complications have been attributable to mild hemoconcentration. In the absence of quantitative blood volume determinations, correction of the masked anemia in chronic shock may be attained by transfusion toward this goal. As demonstrated in Table V, a hematocrit of 50 per cent has consistently indicated restoration of blood volume values to the standard level.

4. *Quantitative Aspects of Transfusion Therapy in Blood Volume Replacement.*—In Table VIII it is shown that in a given case transfusion to replace the estimated deficit may, or may not, restore the blood volume. The first half of the table (VIII-A) records quantitative replacements in patients

with lesions which did not bleed. No evidence of the replenishment of "body storehouses" of hemoglobin, as suggested by Stewart and Warren,¹⁰ was observed. In the latter half of the table (VIII-B) are included patients with protracted gastro-intestinal bleeding and incomplete correction of the blood volume deficit on the basis of quantitative therapy. In Case 324, nearly twice the estimated dosage was necessary. We are in agreement with Emerson and Ebert²¹

TABLE IX
RESULTS OF TRANSFUSION THERAPY IN CHRONIC SHOCK

Case No. and Diagnosis	Transfusion Therapy	Total Cell Volume	Plasma Volume	Blood Volume
		Percentage of Standard		
Case 326.....	Before	38	48	44
Carcinoma of esophagus				
Usual weight 99.8 Kg.	After	114	86	99
Case 306.....	Before	52	85	70
Carcinoma of stomach				
Usual weight 58 Kg.	After	115	94	106
Case 338.....	Before	57	77	68
Carcinoma of esophagus				
Usual weight 77 Kg.	After	109	86	97
Case 322.....	Before	54	77	65
Carcinoma of lung				
Usual weight 103 Kg.	After	108	100	103
Case 335.....	Before	72	83	79
Carcinoma of lung				
Usual weight 79.8 Kg.	After	112	98	104
Case 482.....	Before	45	69	56
Hepatic disease				
Usual weight 68 Kg.	After	109	102	103
Case 480.....	Before	39	95	63
Hepatic disease				
Usual weight 91.6 Kg.	After	91	118	103
Case 481.....	Before	60	66	63
Hepatic disease				
Usual weight 79.4 Kg.	After	95	77	85

that failure of quantitative replacement is a consequence of continued blood loss. It is clinically important to identify these cases for more intensive transfusion therapy followed promptly by corrective surgical procedures.

In chronic shock the plasma volume may be persistently increased following transfusion therapy (Table IX). The observed increase approximates but rarely equals, or exceeds, the gain in red cell volume. It is felt that this observation further supports the concept of a reduced blood volume in chronic shock. A persistent increase in plasma volume after transfusion is at variance with previous observations. It has been generally accepted²⁷⁻²⁹ that blood volume increases two or three days after transfusion are due solely to augmented cell mass because of compensatory return of plasma volume to the pretransfusion level. After transfusion therapy in chronic shock, the increase in plasma volume has been demonstrated to persist for several months.

5. *Tolerance for Surgical Procedures in Patients with Restored Blood Volume.*—Figure 6 illustrates a representative anesthetic record of a properly prepared patient in chronic shock (Patient 306, Table III). This was a 64-year-old man with carcinoma of the stomach, whose initial total hemoglobin and red blood cell volume were approximately 50 per cent of standard for usual weight. Preoperative transfusion of 3,000 Ml. of blood restored the values to standard levels. He underwent a four-hour operative procedure which included gastrectomy, subtotal pancreatectomy, splenectomy, resection of greater omentum, colostomy, and jejunostomy. Three whole blood transfusions of 500 Ml. each were given to replace the blood lost during operation. In spite of this extensive procedure the systolic blood pressure did not vary by

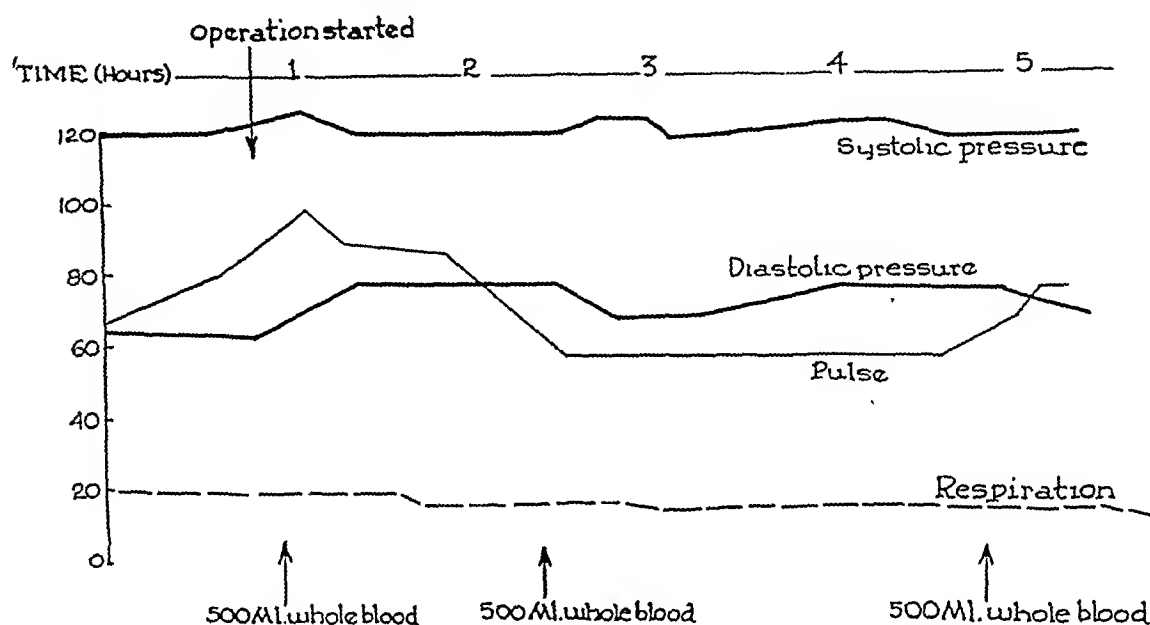


FIG. 6.—Anesthetic record of Case 306. Cyclopropane and ether, endotracheal technic. See text for details.

more than 10 mm. mercury throughout the operative period, and the diastolic pressure remained at, or above, the preoperative level. Pulse rate and respiration also showed minimal fluctuations.

The poor tolerance of the inadequately prepared depleted patient for blood loss during necessary surgical procedures is generally recognized. Abbott,³⁰ and Meyer,³¹ have recommended empirically that blood transfusions be given preoperatively to all patients with peptic ulceration or carcinoma of the colon, even in the absence of anemia. They have attributed to dehydration the nearly normal hemoglobin and hematocrit concentrations observed in these patients. Such a concept of dehydration seems inadequate to explain the established need for blood transfusion in the preoperative preparation of depleted patients.

We have presented evidence that a reduction in blood volume is part of the surgically significant pattern of protein depletion. The significance of the reduced effective blood volume in the patient with weight loss is supported by the unquestionably increased tolerance of the adequately transfused "poor

risk" patient for major surgical procedures. It is further supported by the demonstration of a maintained increase in blood volume prior to significant weight gain during convalescence.

It is doubtful that total restoration of the standard circulating hemoglobin or red blood cell volume is necessary for satisfactory wound healing and convalescence. The critical level of total hemoglobin for optimal synthesis of tissue and plasma protein remains to be evaluated.

SUMMARY AND CONCLUSIONS

1. Reduction in blood volume is part of the surgically significant pattern of protein depletion.

2. Blood volume deficits in depleted patients should be calculated on the basis of standard for usual weight prior to illness.

3. Correction of hemoglobin or red cell deficits by repeated blood transfusion restores the volume to the standard value without producing clinically significant hemoconcentration.

4. During convalescence associated with recovery from disease there is evidence of maintained reestablishment of the blood volume.

5. In the absence of continued bleeding, blood volume replacement by transfusion therapy is quantitative.

6. Quantitative correction of blood volume deficits by whole blood transfusions increases the tolerance of the "poor risk" patients for major surgical procedures.

BIBLIOGRAPHY

- ¹ Whipple, G. H., and Madden, S. C.: Hemoglobin Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies. *Medicine*, 23, 215-224, September, 1944.
- ² Madden, S. C., Kattus, A. A. Jr., Carter, J. R., Miller, L. L., and Whipple, G. H.: Plasma Protein Production as Influenced by Parenteral Protein Digests: Very High Protein Feeding and Red Blood Cell Catabolism. *J. Exper. Med.*, 82, 181-191, September, 1945.
- ³ Fowler, W. M., and Barer, A. P.: Rate of Hemoglobin Regeneration in Blood Donors. *J. A. M. A.*, 118, 420-427, February 7, 1942.
- ⁴ Alstead, Stanley: Rate of Blood-regeneration after Hemorrhagia, *Lancet*, 1, 424-426, April 3, 1943.
- ⁵ Co Tui, Bartter, F. C., Wright, A. W., and Holt, R. B.: Red Cell Reinfusion and Frequency of Plasma Donations: Preliminary Report of Multiple Donations in Eight Weeks by Each of Six Donors. *J. A. M. A.*, 124, 331-336, February 5, 1944.
- ⁶ Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army: Report. *J. A. M. A.*, 123, 1007-1018, December 18, 1943.
- ⁷ Gregersen, M. I.: Practical Method for Determination of Blood Volume with Dye T-1824; Survey of Present Basis of Dye-method and its Clinical Applications. *J. Lab. & Clin. Med.*, 29, 1266-1286, December, 1944.
- ⁸ Varco, R. L.: Preoperative Dietary Management for Surgical Patients. *Surgery*, 19, 303-378, March, 1946.
- ⁹ Lyons, Champ, Mayerson, H. S., Clark, J. H., Nelson, W., and DeCamp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient: I—Concept of Chronic Shock, (in press).
- ¹⁰ Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters. *J. Biol. Chem.*, 115, 63-75, August, 1936.

- 11 Barbour, H. G., and Hamilton, W. F.: The Falling-drop Method for Determining Specific Gravity. *J. Biol. Chem.*, 69, 625-640, August, 1926.
- 12 Weech, A. A., Reeves, E. B., and Goettsch, E.: The Relationship between Specific Gravity and Protein Content in Plasma, Serum and Transudate from Dogs. *J. Biol. Chem.*, 113, 167-174, February, 1936.
- 13 Rowntree, L. G., Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma in Health and Disease. Philadelphia, W. B. Saunders Company, 1929.
- 14 Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume II: Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in 90 Normal Humans. *J. Clin. Investigation*, 16, 317-328, May, 1937.
- 15 Courtice, F. C.: Blood Volume of Normal Animals. *J. Physiol.*, 102, 290-305, December 31, 1943.
- 16 Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume. *Arch. Int. Med.*, 16, 547-576, October, 1915.
- 17 Bock, A. V.: The Constancy of the Volume of Blood Plasma. *Arch. Int. Med.*, 27, 83, January, 1921.
- 18 Davis, L. J.: The Determination of the Blood Volume in Man with Evans Blue ("T-1824"). *Edinburgh Med. J.*, 49, 465-483, August, 1942.
- 19 Stewart, John D., and Warren, Frank: Observations on Severely Wounded in Forward Field Hospitals: With Special Reference to Wound Shock. *ANNALS OF SURGERY*, 122, 129-147, August, 1945.
- 20 Cartwright, G. E., Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients. *J. Clin. Investigation*, 25, 65-80, January, 1946.
- 21 Emerson, C. P., and Ebert, R. V.: Reduced Blood Volume: A Study of Shock in Battle Casualties. *ANNALS OF SURGERY*, 122, 745-772, November, 1943.
- 22 Gregersen, M. I.: Traumatic Shock. *Bull. New York Acad. Med.*, 19, 666, September, 1943.
- 23 Cournand, A., *et al.*: Studies of Circulation in Clinical Shock. *Surgery*, 13, 964-995, June, 1943.
- 24 Richards, D. W., Jr.: Circulation in Traumatic Shock in Man. (Harvey Lecture, February 17, 1944), *Bull. New York Acad. Med.*, 20, 363-393, July, 1944.
- 25 Noble, R. P., and Gregersen, M. I.: Blood Volume in Clinical Shock. I—Mixing Time and Disappearance Rate of T-1824 in Normal Subjects and in Patients in Shock: Determination of Plasma Volume in Man from 10-minute Sample. *J. Clin. Investigation*, 25, 158-171, March, 1946.
- 26 Office of the Surgeon-General, Surgical Consultants Division: Blood Transfusion in the Reparative Management of Battle Wounds. *Bull. U. S. Army Med. Dept.*, 85, 4-5, February, 1945.
- 27 Boycott, A. E., and Oakley, C. L.: Adjustment of Blood Volume after Transfusion. *J. Path. & Bact.*, 38, 91-97, January, 1934.
- 28 Sibley, W. L., and Lundy, J. S.: Blood Volume and Hemoglobin after Transfusion. *Surg., Gynec. & Obst.*, 67, 490-494, October, 1938.
- 29 Kilduffe, R. A., and DeBakey, Michael: The Blood Bank and the Technique and Therapeutics of Transfusions. St. Louis, C. V. Mosby Co., 1942.
- 30 Abbott, W. E., and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients, with Dehydration and Malnutrition; Indications for Intravenous Alimentation with Amino-acids. *Arch. Surg.*, 46, 277-288, February, 1943.
- 31 Meyer, K. A., and Kozoll, D. D.: Primary Resection of the Colon: With Special Reference to Surgical Diagnosis and Management. *S. Clin. North America*, 26, 176-199, February, 1946.

(Continue with Part III)

PART III—QUANTITATIVE ASPECTS OF THE ANEMIA
ASSOCIATED WITH MALIGNANT TUMORS*

Anemia and nutritional depletion are recognized features of neoplastic cachexia. Sachar, and coworkers,¹ and Ariel, and associates,² have emphasized the plasma protein concentration as the best index of reserve body protein. Evans³ has urged determination of the total circulating plasma protein as more informative. It has seemed to us that these considerations of plasma protein as an index of tissue protein reserves neglect the important factor of the other body protein—hemoglobin.^{4, 5} Obviously, it is pertinent to consider the relative deficiencies of both tissue protein and hemoglobin.

Progressive anemia is often more apparent clinically than is the loss of tissue protein in the patient with advancing neoplastic disease. The etiologic factors usually emphasized in the production of this anemia are continued bleeding, interference with nutrition, and metastasis to bone marrow.^{6, 7} There is also good evidence to show that the anemia in malignant disease may result from interference with hemoglobin formation.⁸ Kracke⁹ states that any type of malignancy in any tissue is capable of producing anemia and suggests that the malignant process either elaborates a product capable of bone marrow inhibition or utilizes substances necessary for red cell production. Clark, Power, Heck and Dixon¹⁰ have described a deficiency of iron associated with carcinoma of the proximal portion of the colon. Ewing¹¹ stresses the absorption of hemolytic agents from infected and ulcerating surfaces and from necrosing areas of closed tumors as an important factor. Watson and Young,¹² and Jones and Tillman,¹³ have reported the cure of severe hemolytic anemia following surgical removal of dermoid tumors of the ovary.

Previous studies of the anemia in malignant disease have been primarily concerned with the concentration of red blood cells and hemoglobin.^{10, 14, 15} Ewing,¹¹ however, has stated that most malignant tumors are associated with progressive deterioration in the quality and quantity of the blood. He refers to the work of Louis, in 1846, as showing that the total quantity of the blood is usually much diminished in malignancy. It is the purpose of this report to present observations on the quantity and quality of the circulating blood in patients with malignant disease.

PROCEDURE AND METHODS

Blood volume studies were made under basal conditions in 38 patients hospitalized for treatment of malignant tumors. Serially repeated determinations were made in 23 patients. There were ten patients with carcinoma of the stomach or lower portion of the esophagus, six with carcinoma of the pancreas, four with carcinoma of the colon, and ten with carcinoma of the lung. A miscellaneous group included three patients with sarcoma, two with disseminated carcinomatosis, one with carcinoma of the ureter, one with carcinoma of the breast, and one with widespread mycosis fungoides.

* This is the third report of a series of studies being conducted under a grant from the Research and Development Division, Office of the Surgeon-General, United States Army.

The laboratory determinations were performed in accordance with the technic previously outlined,⁵ the Gregersen method¹⁶ as modified for the Klett-Summerson photo-electric colorimeter being used. Red cell volumes were calculated from hematocrit values obtained after centrifuging heparinized blood for 30 minutes at 3,000 revolutions per minute in Wintrobe tubes. Hemoglobin was determined as oxy-hemoglobin by the photo-electric colorimetric method of Evelyn.¹⁷ Plasma specific gravity was determined by the falling-drop method of Barbour and Hamilton¹⁸ and plasma protein concentration by the formula of Weech, Reeves and Goettsch.¹⁹

The basis for calculation of standard values for the blood volume studies was the patient's usual weight in health.⁵ The diagnosis of malignancy was confirmed in all cases by histologic examination of tissue removed at operation.

EXPERIMENTAL OBSERVATIONS

I. Carcinoma of the Stomach or Lower Portion of the Esophagus: The initial values obtained in ten patients are presented in Table X. The severity of the anemia is graphically illustrated in the averaged alterations from standard (Fig. 7). The red cell mass is markedly reduced, and the cells are deficient in hemoglobin. In contrast to this finding, several of the cases have normal, or nearly normal, total plasma proteins with normal or increased plasma volume. In only one instance (Case 302) was there comparable reduction in total plasma protein and hemoglobin. The high plasma volume recorded is open to variable explanation. Patient 314 had an obstructive lesion of the cardia and had been maintained on high caloric, high protein gastrostomy feedings for three months prior to study. Patient 318 inadvertently received 2,000 Ml. of glucose solution in the 12-hour period prior to study. Patient 325 had concomitant amebiasis and intestinal bleeding. It was impossible to correlate hepatic or other metastases with any pattern of change.

II. Carcinoma of the Pancreas: There were six patients with carcinoma of the head of the pancreas and obstructive jaundice. Two patients (Cases 308 and 332) had primary tumors of the body and tail of the pancreas, with a clinical history of considerable weight loss and progressive anorexia. Both of these latter cases were found to have regional and hepatic metastases at operation. The observations on these six patients are summarized in Table XI. With the exception of one previously transfused patient, there was a deficit of both plasma protein and hemoglobin. In three of the four severely jaundiced patients (Cases 307, 324 and 329), the plasma volume was not significantly reduced from the standard value in spite of considerable weight loss and reduced total plasma protein. In Figure 8 the graphic illustration of the averaged values emphasizes the deficiencies of red cell mass and hemoglobin.

III. Carcinoma of the Colon: The findings in four patients are summarized in Table XII. Patient 316 had multiple hepatic metastases and obstructive jaundice three years after resection. The other patients had early and resectable lesions. The series is too small for separate appraisal, but the averaged

TABLE X
CARCINOMA OF THE STOMACH OR LOWER PORTION OF THE ESOPHAGUS

Case No.	Weight		Hematocrit		Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	% of Standard		% of Standard		% of Standard		% of Standard		% of Standard		% of Standard	
			Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard		
302*	56.7	71.7	41	87	331	36	90	43	1,550	48	1,080	38	2,630	44
304.	76.7	82.6	35	74	348	34	182	76	2,985	80	1,605	49	4,510	66
306.	48.1	58.1	36	76	369	49	146	86	2,205	85	1,240	52	3,445	70
312*	66.2	86.2	44	94	621	56	162	66	2,540	65	1,995	59	4,530	62
314*	53.1	68	28	59	374	43	192	100	3,360	116	1,305	48	4,668	81
318*	49.9	59	24	57	248	33	147	86	3,025	116	960	40	3,985	80
325*	59	72.6	25	59	267	29	193	92	3,865	118	1,300	40	5,155	84
340.	42.6	55.5	37	88	422	61	115	73	2,415	100	1,420	64	3,835	83
338.	64.4	77.1	39	83	521	53	195	89	2,692	77	1,721	57	4,413	68
346.	42.2	55.3	34	72	373	54	196	125	2,967	123	1,120	51	4,087	88
Average.	55.8	68	34	75	387	45	162	83	2,760	93	1,375	50	4,126	73

* Metastases.

TABLE XI
CARCINOMA OF PANCREAS

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	% of Standard		Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard
			Observed	Standard										
307.....	43.1	65.8	38	81	376	46	145	78	2,340	93	1,430	55	3,770	68
308.....	43.5	69.9	41	87	430	49	132	66	2,190	70	1,521	54	3,710	62
315.....	59	97.5	37	78	484	39	183	65	2,630	61	1,542	39	4,170	50
324.....	62.6	70.3	41	87	584	66	119	59	2,915	92	2,030	73	4,945	83
329*.....	49.4	61.2	39	83	513	65	210	120	2,675	99	1,715	69	4,387	85
332.....	60.3	74.8	45	96	585	62	163	76	2,315	68	1,895	64	4,205	66
Average.....	53	73.3	40	85	495	55	159	77	2,510	80	1,690	59	4,200	69

* 1,000 Ml. blood transfused 18 days prior to determination.

CHRONIC SHOCK

TABLE XII
CARCINOMA OF COLON

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard
303.....	54.9	72.6	39	83	524	57	199	90	2,760	86	1,760	62	4,520	75
316*.....	52.2	64.4	36	86	338	42	60	33	1,975	71	1,110	44	3,085	57
321.....	72.6	81.6	40	95	430	42	197	86	2,430	66	1,620	50	4,055	58
341.....	60.3	74.8	36	86	446	47	168	78	2,480	73	1,396	48	3,875	61
Average.....	60	73	38	87.5	435	47	156	72	2,410	74	1,470	51	3,885	63
* Metastases.														

TABLE XIII
CARCINOMA OF THE LUNG

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard
305*.....	57.6	67.9	38	81	451	52	148	74	2,410	80	1,465	53	3,880	68
313*.....	54.4	65.8	37	76	451	55	200	108	2,915	103	1,640	63	4,560	82
322*.....	89.4	103.4	49	104	756	96	234	77	3,490	77	2,230	54	5,715	65
323*.....	55.3	61.2	43	91	849	77	141	80	2,695	100	2,590	105	5,285	102
328.....	65.8	86.2	43	96	698	70	252	103	3,810	83	2,875	81	6,685	91
331*.....	65.8	77.1	43	91	729	85	176	80	2,905	97	2,190	73	5,095	78
333*.....	62.6	68	38	81	503	58	198	100	2,825	96	2,310	85	5,135	90
334*.....	56.7	68	43	91	657	65	136	73	2,785	83	1,710	63	4,490	78
335.....	72.6	79.8	41	88	522	47	203	84	2,995	76	2,260	72	5,255	79
336*.....	63	84.4	41	88	628	65	188	86	2,849	89	2,101	70	4,580	64
Average.....	64	76.2							2,967				5,068	80
* Metastases.														

values shown in Figure 9 suggest conformity with other lesions of the gastrointestinal tract.

IV. Carcinoma of the Lung: The determinations on ten patients included in this series are summarized in Table XIII. In five patients (Cases 313, 323,

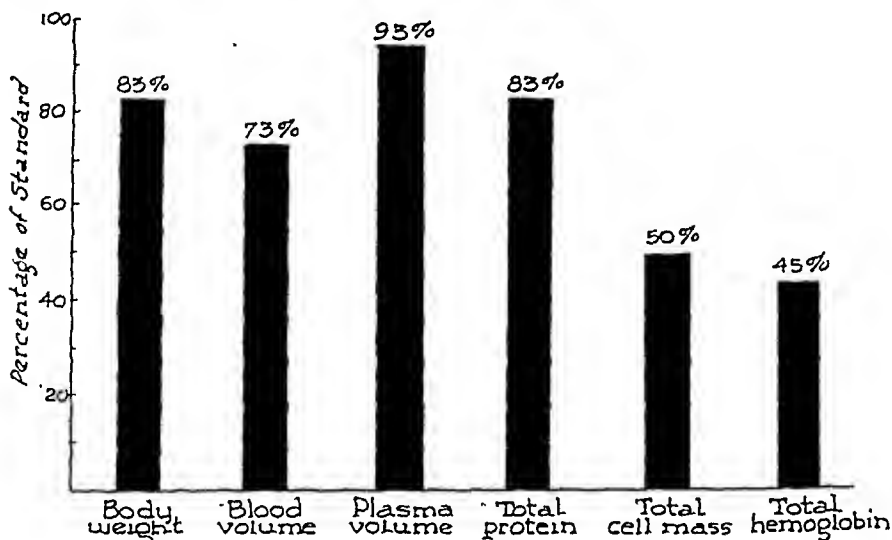


FIG. 7.—Blood volume determinations in carcinoma of the stomach or lower portion of the esophagus. Averages for ten cases.

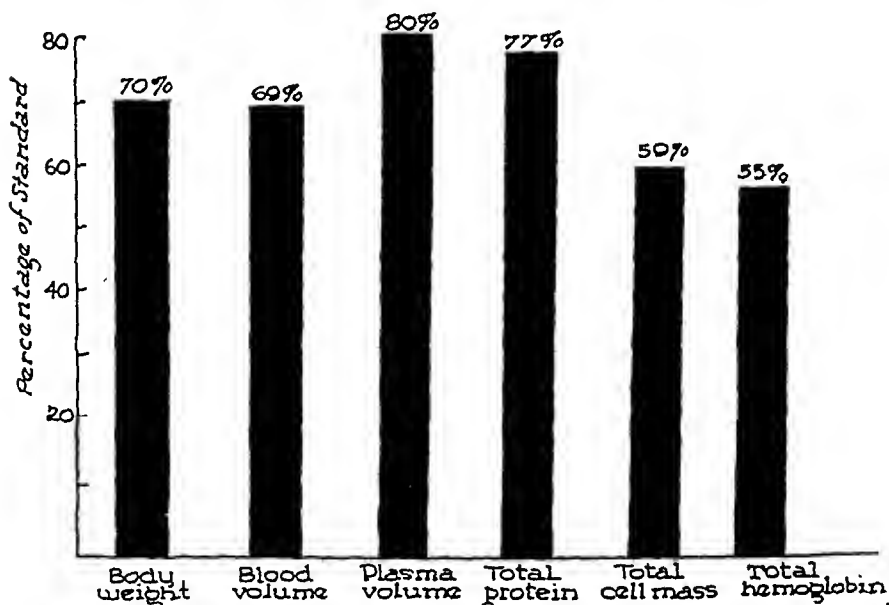


FIG. 8.—Blood volume determinations in carcinoma of the pancreas. Averages for six cases.

328, 333 and 334) the plasma volume was not significantly reduced. The averaged values, as shown in Figure 10, again emphasize the greater deficit in cell mass and hemoglobin as compared to plasma protein.

V. Miscellaneous Malignancies: The studies on these eight patients are

summarized in Table XIV: The findings are of interest, insofar as they illustrate the greater deficiency of hemoglobin as compared to plasma protein.

Discussion.—The deficits observed in patients with malignant disease of the lower portion of the esophagus, the stomach, pancreas, and colon were

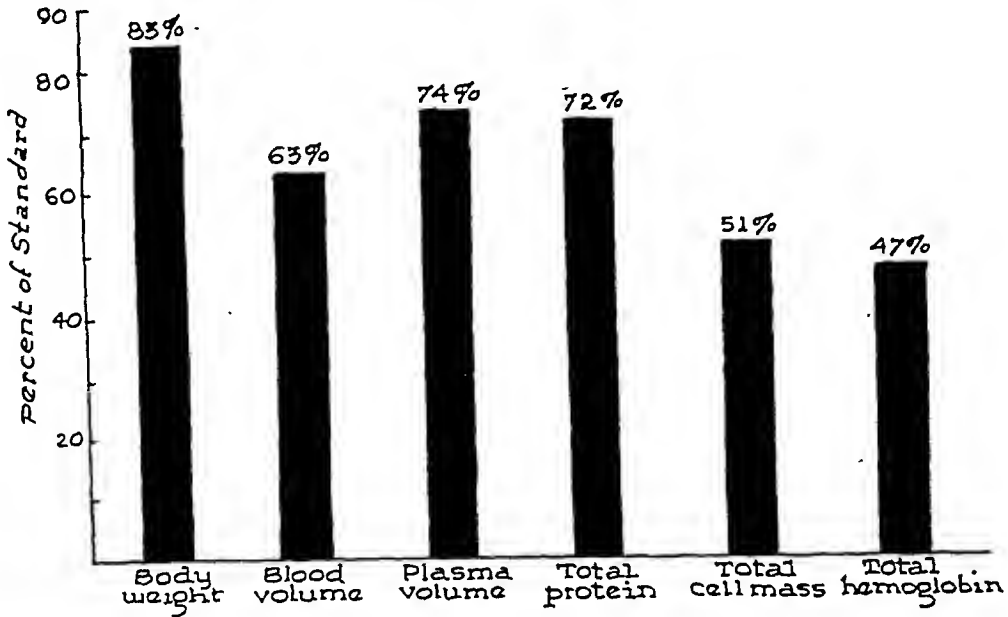


FIG. 9.—Blood volume determinations in carcinoma of the colon. Averages for four patients.

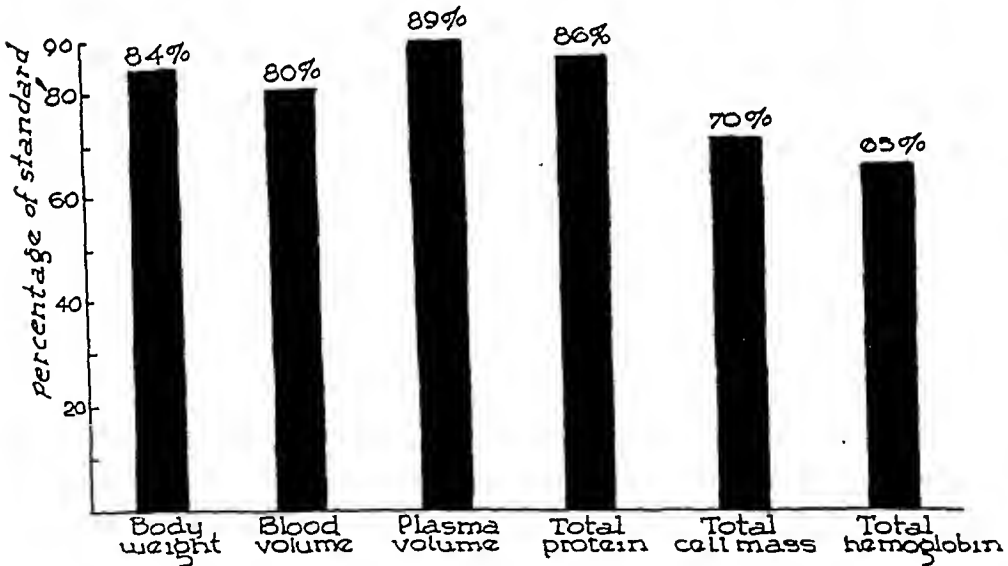


FIG. 10.—Blood volume determinations in carcinoma of the lung. Averages for ten patients.

essentially of the same magnitude. However, as would be expected, the deficits in patients with carcinoma of the lung were less marked. In this condition bleeding is less frequent, and there is no direct interference with nutrition.

It is apparent from our studies that the major factor responsible for the reduced blood volume is a deficiency of total circulating red cell mass and hemoglobin. These findings are in agreement with those of Taylor, and his colleagues,^{20, 21} who reported evidence that tumor tissue implanted into mice and developing chicks results in marked depression of blood hemoglobin con-

centration in the host. These authors²² also reported an early decrease in blood volume associated with a progressive decrease in total hemoglobin when tumor tissue was implanted into mice.

TABLE XIV
MISCELLANEOUS MALIGNANCIES

Case No. and Diagnosis	Weight	Hem- atocrit	Total Hemo- globin	Total Plasma Protein	Plasma Volume	Total Cell Volume	Blood Volume
Percentage of Standard for Usual Weight							
309—Osteosarcoma, with pulmonary metastases,	79	72	48	96	99	60	82
310—Angiosarcoma of femur. . .	86	62	40	110	105	41	77
319—Lymphosarcoma,	87	100	75	95	92	83	88
342*—Mycosis fungoides, with multiple metastases,	83	94	67	44	75	67	71
337—Carcinoma of ureter,	78	87	79	95	100	78	90
320—Carcinoma of breast,	100	89	58	100	94	60	78
311—Adenocarcinoma, with liver metastases; primary probably in bowel,	91	95	42	61	60	44	53
301—Adenocarcinoma, with generalized metastases; primary probably in bowel, . .	62	68	41	98	79	41	60

* 1,500 MI. blood two weeks prior to determination.

The deficit of plasma volume was usually considerably less than that of the red cell mass, and showed a range of from 48 per cent to 123 per cent of standard. Because of this variation the hematocrit proved totally unreliable as an index of the degree of hemoglobin deficit. In general, the plasma volume correlated with the total plasma proteins and gave evidence of maintenance of their usual osmotic affinity. From this it would seem that the changes observed in malignant disease are the result of deficiencies in red cell mass and hemoglobin without consistent depletion of tissue protein reservoirs. Furthermore, since anemia may persist in spite of forced high protein feedings (Patient 314), we are reluctant to accept the point of view of Varco,²³ and others,²⁴ that a high dietary intake of protein is the factor of primary importance in the preoperative preparation of patients with malignant disease. Although this factor is unquestionably of importance, adequate preoperative therapy demands correction of anemia by means of whole blood transfusions.⁵ In malignant disease, as in chronic sepsis,²⁵ there is a fundamental disturbance in hemoglobin metabolism. The nature of this disturbance remains to be elucidated.

SUMMARY

1. Blood volume studies in 38 patients with malignant disease are presented.
2. The major factor responsible for the reduced blood volume associated with malignant disease is a deficiency of total circulating cell mass and hemoglobin.
3. In malignant disease there is a fundamental disturbance in hemoglobin metabolism.
4. Adequate preoperative preparation of patients with malignant disease can be accomplished only by transfusion replacement therapy.

The technical assistance of Miss S. E. Burt is gratefully acknowledged.

BIBLIOGRAPHY

- ¹ Sachar, L. A., Horvitz, A., and Elman, R.: Studies on Hypoalbuminemia Produced by Protein-deficient Diets: Hypoalbuminemia as Quantitative Measure of Tissue Protein Depletion. *J. Exper. Med.*, 75, 453-459, April, 1942.
- ² Ariel, I., Rekers, P. E., Pack, G. T., and Rhoades, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: Hypoproteinemia and Anemia in Patients With Gastric Cancer. *ANNALS OF SURGERY*, 118, 366-371, September, 1943.
- ³ Evans, E. I.: Significance of Blood Volume Alterations in Surgical Patients. *South. M. J.*, 38, 214-221, March, 1945.
- ⁴ Lyons, C., Mayerson, H. S., Clark, J. H., Nelson, W., and DeCamp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient: I. Concept of Chronic Shock. (In Press)
- ⁵ Clark, J. H., Lyons, C., Mayerson, H. S., Nelson, W. and DeCamp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient: II. Hemoglobin and Red Blood Cell Deficits in Chronic Shock. (To be published)
- ⁶ Wintrobe, M. M.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942.
- ⁷ Castle, W. B., and Minot, G. R.: *Pathologic Physiology and Clinical Description of the Anemias*, New York, Oxford University Press, 1936.
- ⁸ Oppenheim, A., Abels, J. C., Pack, G. T., and Rhoades, C. P.: Metabolic Studies in Patients with Cancer of Gastrointestinal Tract: Anemia of Patients with Gastric Carcinoma. *J. A. M. A.*, 127, 273-276, February, 1945.
- ⁹ Kracke, R. R.: *Disease of the Blood*, Philadelphia, J. B. Lippincott Co., 1941.
- ¹⁰ Clark, R. L., Power, M. H., Heck, F. J., and Dixon, C. F.: Iron Deficiency and Anemia Associated with Carcinoma of Proximal Portion of Colon. *M. Clin. North America*, 29, 958-975, July, 1945.
- ¹¹ Ewing, J.: *Neoplastic Diseases*. Philadelphia, W. B. Saunders Co., 1940.
- ¹² Watson, W. N. W., and Young, C. J.: Failed Splenectomy in Acholuric Jaundice, and Relation of Toxemia to Hemolytic Crisis. *Brit. M. J.*, 1, 1305-1309, June, 1938.
- ¹³ Jones, E., and Tillman, C.: Case of Hemolytic Anemia Relieved by Removal of an Ovarian Tumor. *J. A. M. A.*, 128, 1225-1227, August, 1945.
- ¹⁴ Morrison, M.: Analysis of Blood Picture in 100 Cases of Malignancy. *J. Lab. & Clin. Med.*, 17, 1071-1093, August, 1932.
- ¹⁵ Isaacs, R.: Anemia in Cancer. *M. Clin. North America*, 10, 1219-1233, March, 1927.
- ¹⁶ Gregersen, M. I.: Practical Method for the Determination of Blood Volume with the Dye T-1824: Survey of Present Basis of Dye Method and Its Clinical Applications. *J. Lab. & Clin. Med.*, 29, 1266-1286, December, 1944.
- ¹⁷ Evelyn, K. A.: Stabilized Photo-electric Colorimeter with Light Filters. *J. Biol. Chem.*, 115, 63-75, August, 1936.
- ¹⁸ Barbour, H. G., and Hamilton, W. F.: The Falling-drop Method for Determining Specific Gravity: Clinical Applications. *J. A. M. A.*, 88, 91-94, January, 1927.
- ¹⁹ Weech, A. A., Reeves, E. B., and Goettsch, E.: Relationship between Specific Gravity and Protein Content in Plasma, Serum and Transudate from Dogs. *J. Biol. Chem.*, 113, 162-174, February, 1936.
- ²⁰ Taylor, A., and Pollack, M. A.: Hemoglobin Level and Tumor Growth. *Cancer Research*, 2, 223-227, March, 1942.
- ²¹ Taylor, D. R., McAfee, M., and Taylor, A.: The Effect of Yolk Sac-cultivated Tumors on Hemoglobin Level in Embryonic Chick. *Cancer Research*, 3, 542-545, August, 1943.
- ²² Taylor, A.: Changes in Hemoglobin Concentration, Total Hemoglobin, and Blood Volume Associated with Tumor Growth. *Cancer Stud.*, Texas Publ., Pp. 95-102, February 15, 1945.
- ²³ Varco, R. L.: Preoperative Dietary Management for Surgical Patients. *Surgery*, 19, 303-378, March, 1946.

- ²⁴ Lund, C. C., and Levenson, S. M.: Protein in Surgery. J. A. M. A., 128, 95-100, May, 1945.
- ²⁵ Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army: Report. J. A. M. A., 123, 1007-1018, December, 1943.

DR. WILLIAM H. PRIOLEAU, Charleston, S. C.: Since hearing Doctor Lyons' presentation of this subject this fall in New Orleans I have endeavored to put into practice his concept of chronic shock. In so doing several questions have arisen, particularly with regard to over-transfusion. In such case what is the fate of the red cells? Is there danger of their breaking down and occluding the renal tubules? Is there an increased tendency toward blood clotting, with resultant occlusion of capillaries?

DR. EVERETT I. EVANS, Richmond, Va.: I rise to comment on Doctor Lyons' paper mainly because of our keen interest for five or six years in the acute shock problem. First, I think we must question the propriety of the term "chronic shock." Those who have suffered castigation at the hands of one or two writers in Philadelphia and New York, know how careful one has to be in the proper use of terms. If we keep in mind what Doctor Lyons is doing, that he is dealing with reduced blood volume, perhaps we can safely use the term, but let us not go back to considering surgical shock as due to many causes.

I should like to refer to our work on 240 patients coming in for more or less routine elective surgery. As we took these patients and estimated their blood volume, the 240 so-called normal patients (whose figures on routine examination showed protein about 7 per cent and hemoglobin about 14.5 Gm.) we found a great number of patients who fell out of the normal range; in other words, some patients can apparently be well and have a plasma volume as low as 19 cc. per kilogram (about 33 per cent of normal). When one considers the total circulating hemoglobin, there may be found even worse situations. Blood volume in some of these patients was so depressed that although many of them showed a normal hemoglobin by routine laboratory test, actually, 85 per cent of these patients had a total circulating hemoglobin below accepted normal values. This simply substantiates everything Doctor Lyons pointed out to you, the extreme importance of estimating hemoglobin according to the total circulating amount and not be falsely led by simple laboratory data for hemoglobin. If you will follow out these plans as laid down by Doctor Lyons, you should be able to operate upon a great many more patients who would not be able to withstand even simple anesthesia without operation if the blood volume were not restored.

I am certain that if you will apply these blood volume methods in your hospital practice, you will improve greatly the postoperative and pre-operative care of patients. Finally, I think that in all teaching hospitals it would be a very good thing if we could interest one or two young surgeons in blood volume technic. I know of nothing that will focus more properly attention on the true causes of cardiovascular failure than attention to our knowledge of blood volume matters. Attention to blood volume and cardiac output data will focus attention properly on physiologic phenomena. In most clinical shock the true cause will be determined and we will not fall into the error of believing it due to errors in technic, toxins, etc.

I think Doctor Lyons is to be congratulated in this important work.

DR. CHAMP LYONS, New Orleans, La. (closing): I am most grateful for the comments of the discussers. I can answer Doctor Prioleau's question by saying we have had trouble in finding enough blood to give to these patients. In general, we have adhered to a daily limit of 1,000 cc. of blood for a patient with an hematocrit below 40, and 500 cc. of blood for a patient with an hematocrit above 40, in the absence of concomitant blood loss. In some of our experiments we have deliberately chosen to provide an excess of red blood cells. There has been no evidence of untoward effect or overloading of the vascular system in all our experiences.

THE TREATMENT OF INJURIES OF THE BRACHIAL PLEXUS*

LOYAL DAVIS, M.D., JOHN MARTIN, M.D.,

AND

GEORGE PERRET, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL.

TRAUMATIC LESIONS which involve parts of the brachial plexus are not uncommon in civilian and military life. They may be the result of penetrating stab or bullet wounds, or more commonly in civil life, are produced by blunt trauma upon the side of the neck with the head flexed far to the opposite side and the shoulder depressed (Fig. 1). Birth palsies result from injury to the brachial plexus or its roots during parturition, especially in breech deliveries, and the mechanism of the trauma is the same. The chief factor is overstretching and traction upon one or more components of the plexus produced by any means which force the head and shoulder apart. The extent of the lesions depends upon the violence with which the nerve roots, cords or trunks have been stretched and pulled (Fig. 2), so that any degree of injury may be found in the same patient extending between the extremes of incomplete physiologic block and complete anatomic interruption of continuity.

Blunt injuries differ from stab or gunshot wounds in that the nerve fibers are not severed in a well-defined place, but are torn apart. The overstretched funiculi may rupture at any point from the origin of the roots from the spinal cord to the most distal portion of the injury. Therefore, some fibers may be avulsed, others torn apart within the nerve trunks, and others overstretched. The resulting clinical symptoms are those of complete and incomplete anatomic or physiologic lesions which cannot and should not be catalogued according to the early classification of brachial plexus injuries into the upper (Erb) or lower (Klumpke) types. We believe it is far more accurate and practical to determine the extent of the paralysis by careful, detailed examinations of the muscles and then place the level of the lesion by a knowledge of the innervation of those muscles (Fig. 3a, b). The progress of recovery can be followed more easily and a final evaluation of the residual lesion can be made accurately.

Rupture is most frequent in those portions of the plexus which are subjected to the greatest stretch, that is in the 5th and 6th cervical spinal nerves. Avulsion of the roots from the spinal cord is less frequent, and when it occurs, spinal cord symptoms are usually present. The lower roots and spinal nerves which contribute to the plexus; *i.e.*, cervical 7, 8 and thoracic 1, are less often injured and exhibit more evidence of spontaneous recovery. In stab

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

or bullet wounds, the most exposed portions of the plexus are usually injured: *i.e.*, the 5th, 6th and 7th cervical nerves and the upper trunk of the plexus, in their course from the spinal column between the anterior and medial scalene muscles. In axillary and infraclavicular wounds the individual nerves which arise from the cords of the plexus and the larger blood vessels are more likely to be injured. We have shown experimentally that bullet or other high velocity missiles have an additional concussive effect which may produce varying degrees of paralysis. Thus, immediately following injury, it is practically impossible to determine accurately the completeness of a brachial plexus injury until an interval has elapsed.

Injury to the contributing spinal nerves close to their exit from the intervertebral foramina or to the upper, middle and lower nerve trunks produces a segmental distribution of the motor and sensory disturbances. The paralyzed muscles fall into groups which correspond with the nerve roots

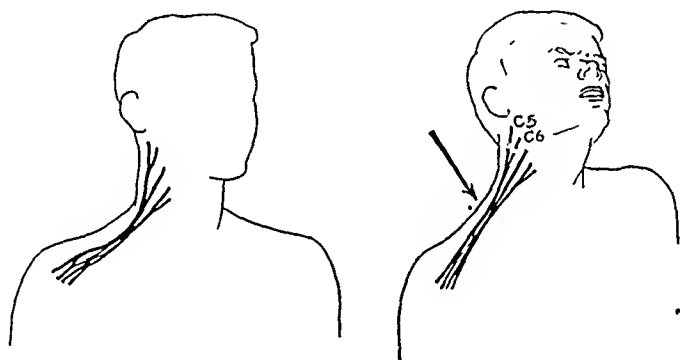


FIG. 1.—Diagram showing the mechanism of production of brachial plexus lesions by blunt injury.

from which they derive their innervation. Thus, injury to 5th and 6th cervical spinal nerves and the upper trunk will affect chiefly the muscles of the shoulder girdle and the upper portion of the extremity. Injuries to the 7th and 8th cervical and 1st thoracic spinal nerves, and middle and lower trunks, produce the greatest disability in the forearm and hand. Injury to the 1st thoracic root or spinal nerve may be accompanied frequently by a Horner's syndrome. Lesions of the cords produce symptoms more closely related to the peripheral nerve pattern of motor and sensory loss. Involvement of the lateral cord produces paralysis in the distribution of the musculocutaneous and upper portion of the median nerves. Medial cord injuries affect the areas supplied by the ulnar, medial cutaneous of the arm and forearm and the lower portion of the median nerve. The radial, axillary, subscapular and thoracodorsal nerves are completely or partially involved depending on the location of the injury to the posterior cord. However, especially in blunt injuries, more than one component of the brachial plexus is involved; trunks or cords may be partly injured and compression and pull may be produced by hemorrhage, infection or an aneurysm. Subsequent extensive scar tissue formation tends to impair

INJURIES OF BRACHIAL PLEXUS

to various degrees many originally uninjured portions of the plexus and gives rise to disseminated and incomplete motor and sensory disturbances.

We have studied 47 cases of brachial plexus injury, 30 of which were produced by high velocity missiles or stab wounds and the remaining 17 by blunt trauma. Twenty-two of the patients were injured in civilian life and 25 while in military service. In six patients there was an associated injury of the spinal cord.

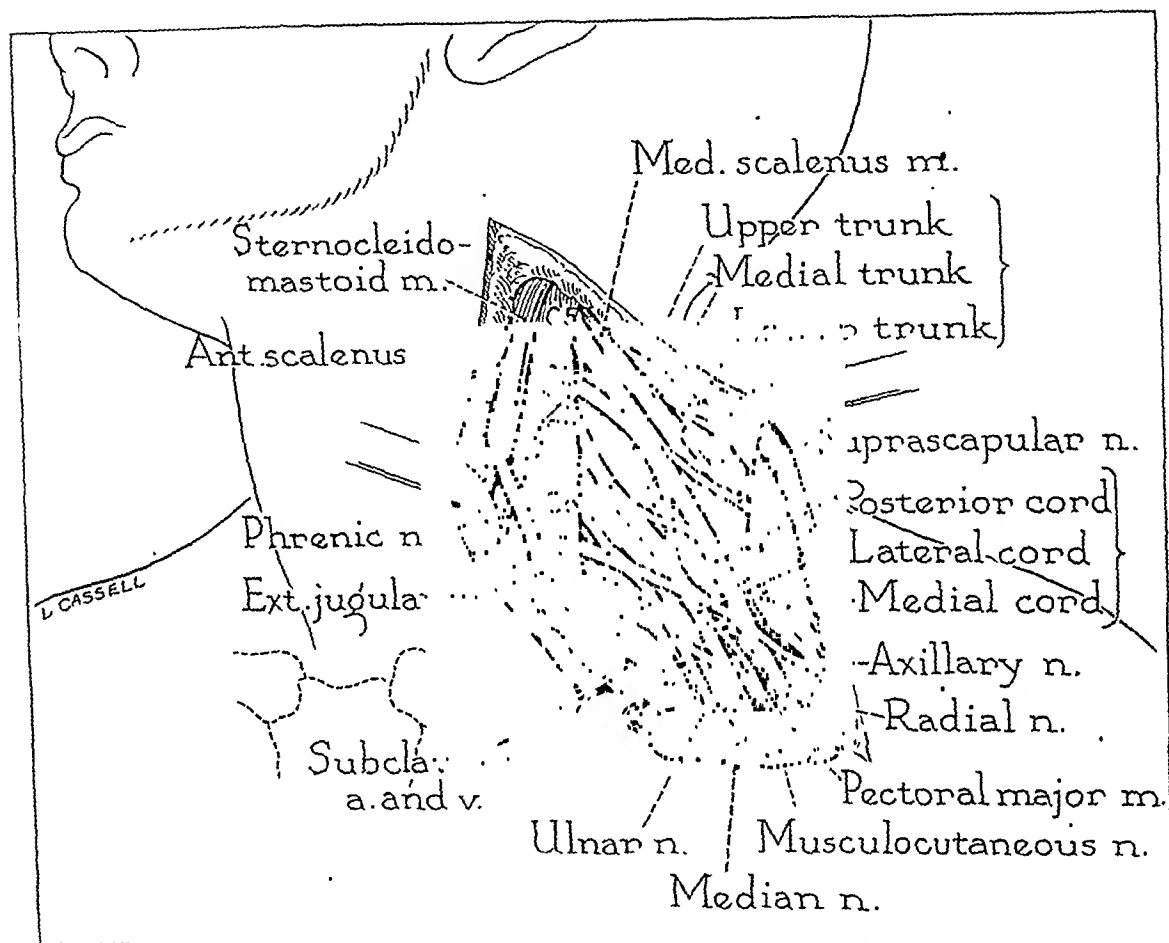


FIG. 2.--Schematic drawing of the main components of the brachial plexus.

The length of time which elapsed between the injury and examination of the patients varied considerably. Usually, lesions due to penetrating wounds were observed at an earlier date after injury than those due to blunt injury, many of which did not seek active medical treatment for periods of three, five and even eight years after injury.

A study of the segmental level of the lesion in this group of patients shows that the 5th cervical fibers were involved 21 times; the 6th cervical 27 times; the 7th cervical 26 times; the 8th cervical 29 times, and the 1st thoracic 18 times. Complete avulsion of the roots from the spinal cord was observed in only two cases following severe automobile accidents and they were associated with spinal cord lesions. Injury to the upper trunk was diagnosed in 11 cases (five blunt, three stab and three bullet injuries), to the upper and middle

trunks in two cases, to the lower trunk in four cases, and to all three in one case. The medial cord was involved in nine cases of gunshot origin; the lateral cord in one case; the posterior cord in four cases; the posterior and lateral cords in two cases, and the medial and posterior cords in four patients. Eleven

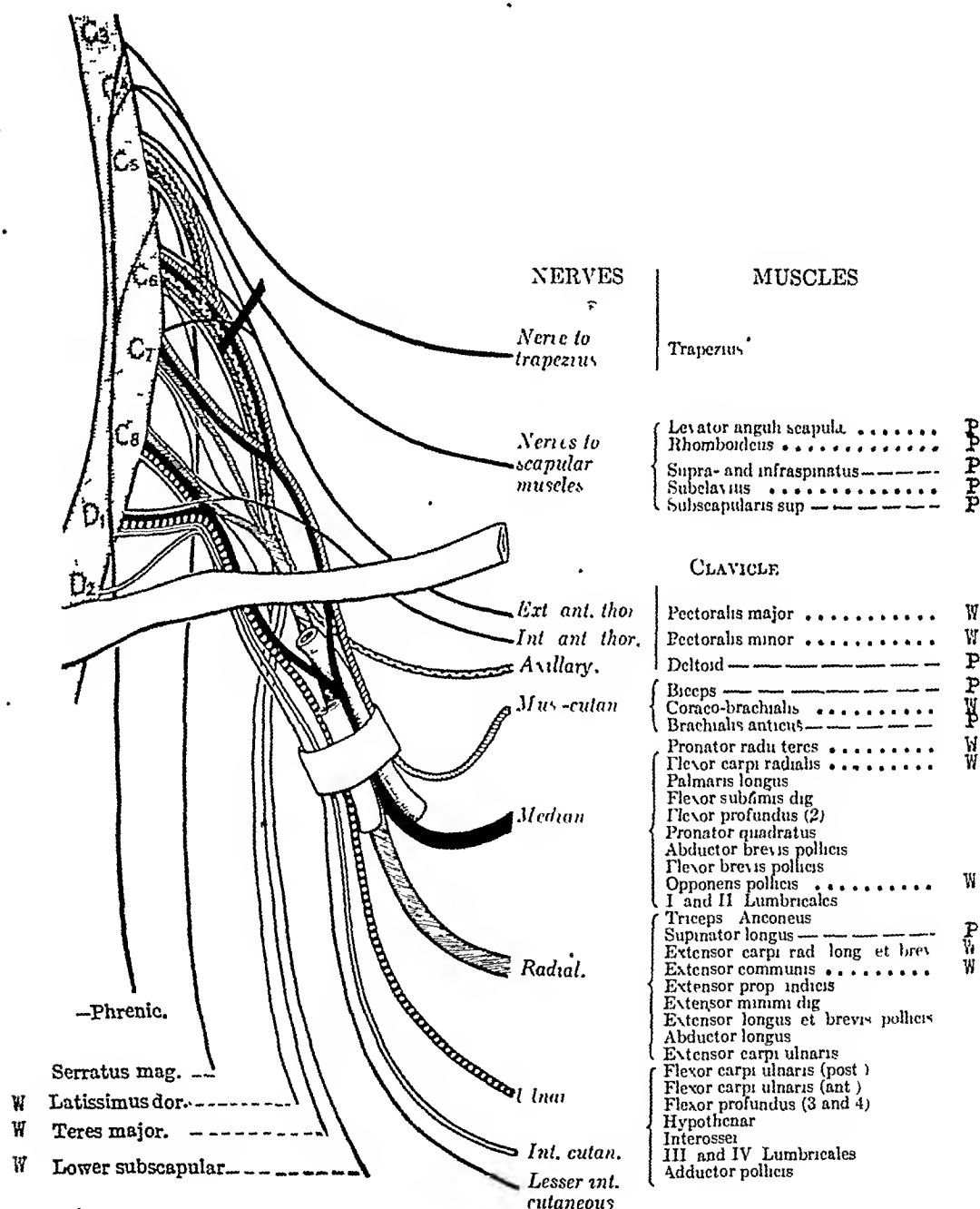


FIG. 3-A

FIG. 3—(A) Diagram showing the muscles involved in a typical blunt brachial plexus injury

INJURIES OF BRACHIAL PLEXUS

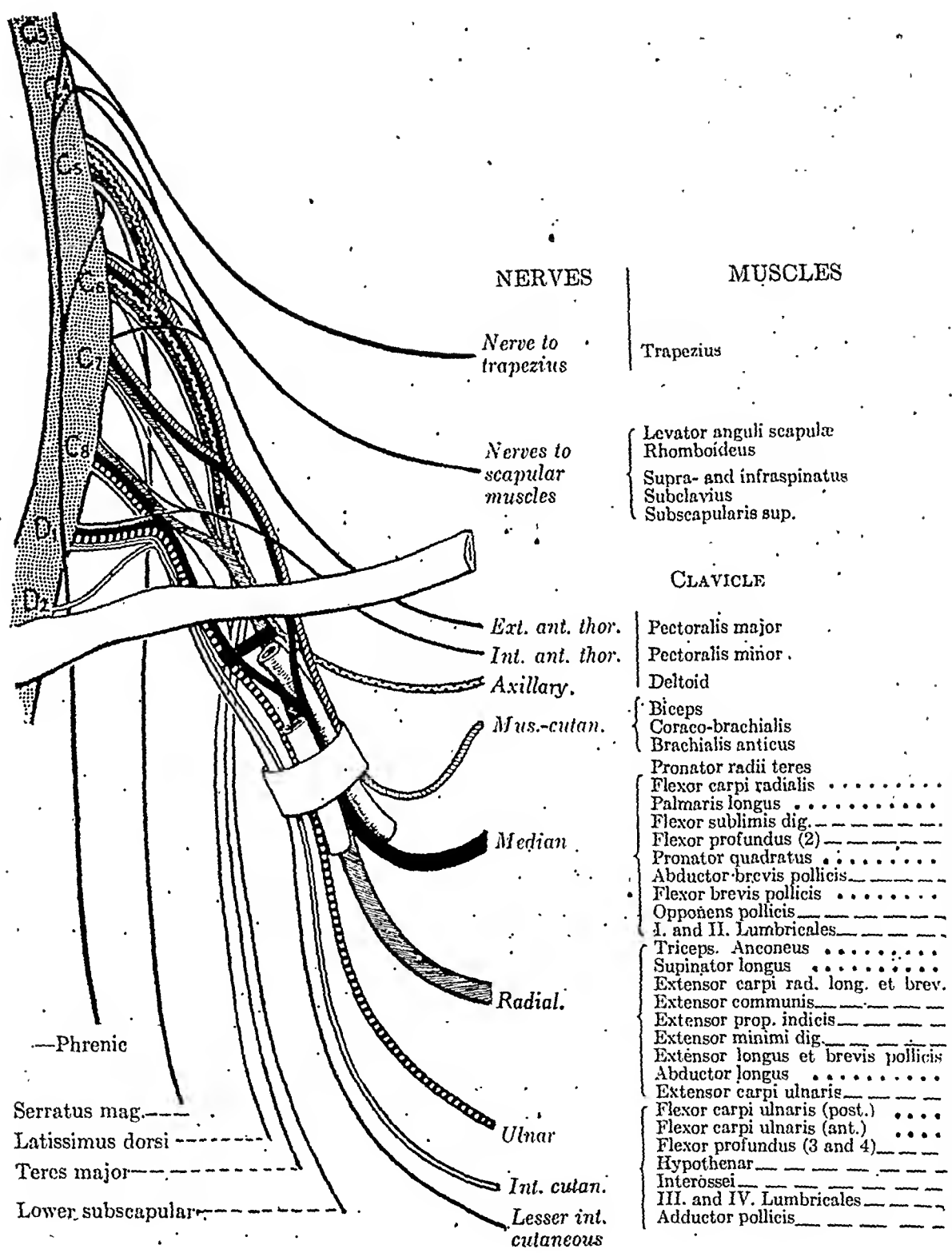


FIG. 3-B

FIG. 3.—(B) Diagram showing the muscles involved in a common infraclavicular gunshot injury of the brachial plexus.

of the lesions to the primary nerves and trunks were due to blunt stretch injuries and in six cases to stab wounds. Blunt trauma caused lesions to the cords of the plexus in five instances only, while 15 were due to gunshot injuries. There was one tardy paralysis, involving the ulnar nerve, which was produced by traction on the medial cord of the plexus by the weight of the arm whose shoulder joint had been completely removed by a shell fragment.

Table I summarizes the portions of the plexus found to be injured and the kind of injury reported in this series.

TABLE I
SUMMARY SHOWING PORTIONS OF PLEXUS INJURED
AND THE TYPE OF INJURY

Parts of Plexus Injured	Blunt	Gunshot	Stab
Roots (avulsion).....	2
Nerves, C 5.....	2
C 6 and C 7.....	..	1	..
C 7 and C 8.....	..	1	..
Trunks, upper....	5	3	3
Upper and middle....	2
Lower.....	1	2	1
Upper, middle and lower....	1
Cords, lateral.	1	..
Medial.....	..	9	..
Posterior.....	2	2	..
Lateral and posterior. .	2
Medial and posterior .	1	3	..
Incomplete lesions ..	1	2	..

Associated injuries to the surrounding tissues were frequent. The clavicle was fractured in 11 cases, eight times following bullet wounds and in three instances after blunt trauma. The humerus was fractured and the shoulder joint disrupted in four cases of gunshot injuries. Fractures of part of the 5th and 6th cervical vertebrae were observed in one case following blunt injury and in one bullet wound. Associated severe spinal cord injuries were present in six patients, and in two associated cerebral symptoms were noted. In three cases the recurrent laryngeal nerve was injured on the side of the plexus lesion, and a Horner syndrome was observed in three patients. An aneurysm of the subclavian artery was present in four patients.

As a rule, immediately following the initial trauma to the brachial plexus the entire affected extremity is paralyzed and anesthetic. A physiologic lesion may recover spontaneously and fairly rapidly. In all types of brachial plexus injuries, physiotherapy should be instituted at once and should be systematic and continuous over a long period of time, sometimes years. An attempt should be made to prevent contractures and deformities by proper splinting, massage and passive and active movements. Useful supplementary movements performed by unaffected muscles should be developed and when all evidence of regeneration and spontaneous recovery have ceased, or are unsatisfactory, surgical repair should be considered and carefully evaluated.

The indications for operation on the plexus vary greatly with each individual case and especially when the injury is due to blunt trauma. Signs of spontaneous recovery must be determined for the individual nerve roots and

spinal nerves because the less damaged may regenerate and the more severely damaged ones may show no signs whatever of regeneration. Taylor,⁷ who studied a large group of obstetrical brachial palsies, advised operation six to 12 months after the injury, depending on the amount of spontaneous recovery that had taken place and the severity of the lesion. While a large number of physicians consider brachial plexus lesions as irreparable and hopeless, most neurologic surgeons advise early surgical treatment. The outlook for recovery of function is much improved with prompt surgical repair. As time goes on, scar tissue becomes denser and constricts the plexus more and more, retarding and stopping all possibilities of nerve fiber regeneration. At the same time muscle atrophy progresses, joint changes occur, and in old neglected cases the only method to obtain some function lies in plastic operations upon tendons or joints.

Every attempt should be made to liberate the plexus from the surrounding scar tissue by freeing and identifying the individual roots, trunks, cords and nerves, to resect the scar tissue and neuromas and to obtain an end-to-end union of the ruptured nerves. This is often difficult, and at times impossible, because of the amount of scar tissue and contractions present, especially in old neglected lesions, or when the roots are avulsed from the spinal cord or torn within or near the intervertebral foramina. The experimental promise of properly used nerve grafts is particularly applicable to these injuries. The use of nerve grafts may be indicated where a loss of nerve substance is present and when end-to-end apposition is not possible. Autogenous grafts of the desired size are rarely available and consequently fresh homogenous grafts should be used. In some instances resection of the middle third of the clavicle will make it possible to secure a better end-to-end apposition of the severed nerve segment. It has also been suggested that the severed distal segments of the 5th or 6th cervical roots which can not be sutured to their proximal segments, be sutured to the sectioned ansa hypoglossi. At operation, the entire brachial plexus should be explored, the anterior scalene muscle and the clavicle divided if necessary, and proper electrical stimulation of the exposed nerves employed to detect the injured nerves. Neurolysis was performed in 20 of the 22 civilian patients and in three, end-to-end suture of the severed 5th cervical spinal nerve, or the upper trunk was performed. Bone and metallic fragments which encroach upon the plexus should be removed, and in our cases of aneurysm of the subclavian artery, the artery was ligated without any untoward effect.

In old neglected lesions, the scar tissue may be so dense that even neurolysis becomes impossible and the segments of the severed nerves can not be identified, or the plexus roots are avulsed from the spinal cord making suture impossible. In such cases no improvement in function can be expected from the exploration of the brachial plexus. However, other surgical procedures should be used to obtain the optimal position of function for the extremity. The most gratifying result follows the shortening of tendons of paralyzed muscles or the implantation of tendons of normal muscles into the distal tendons of paralyzed muscles. These plastic operations help to bring the hand,

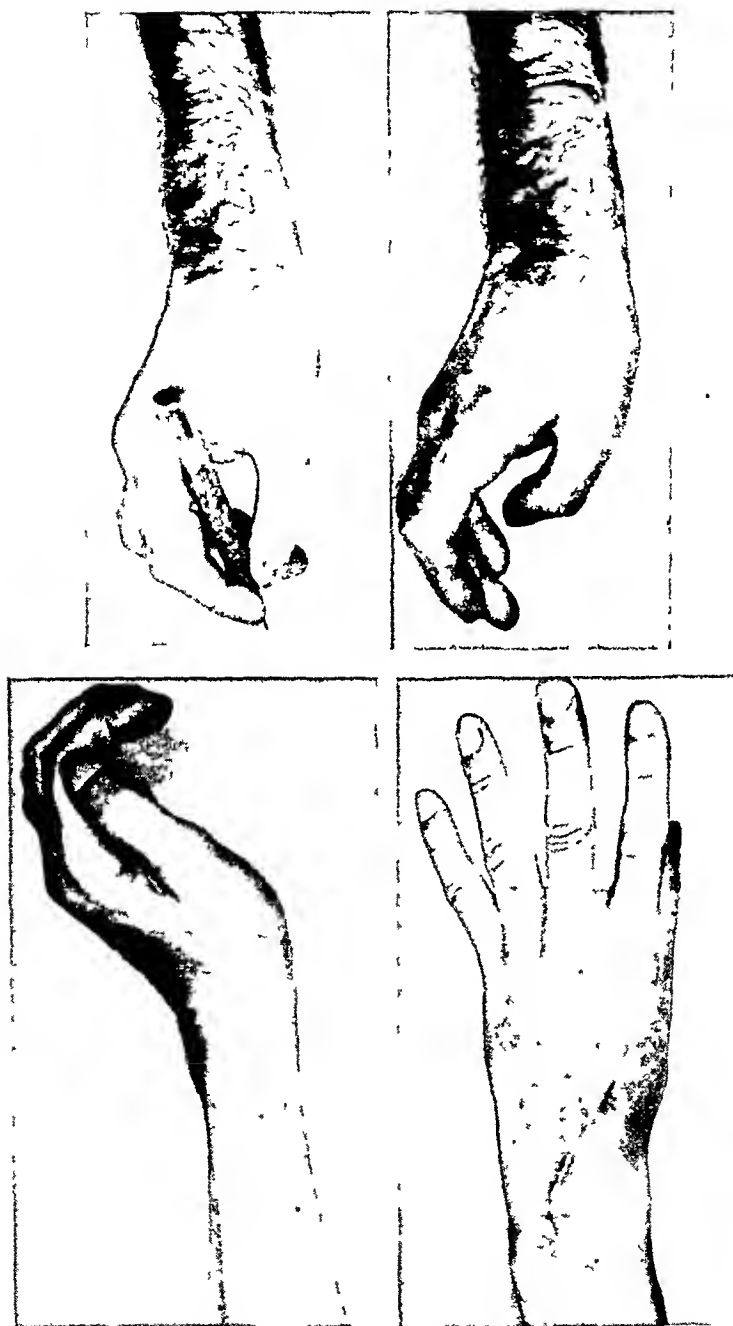


FIG 4—Position of function of the hand following tendon transplantations to overcome paralysis of the extensor muscles of the fingers and wrist

for example, into a position of optimal usefulness, or may bring about some dorsiflexion in a hand of an extremity in which all of the extensor muscles are completely atrophied and fibrosed. Shortening of the tendons of overstretched paralyzed muscles and implantation of normal tendons into paralyzed ones has been undertaken in five of the 47 patients. They all had irreparable injuries of several years' duration—two of them of eight years' duration—and

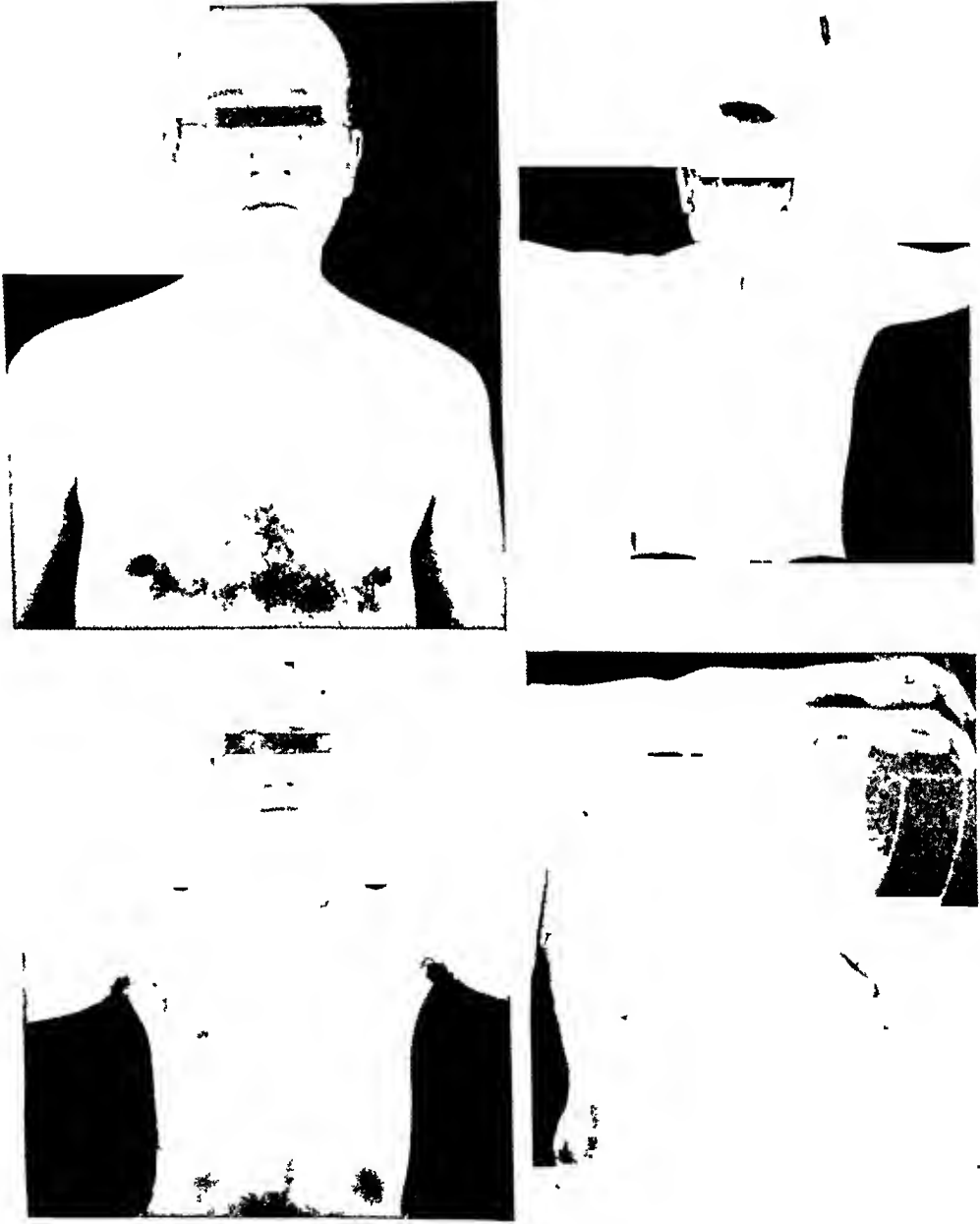


FIG. 5.—Supplementary movements which permit abduction of the arm following a lesion of the 5th and 6th cervical nerves, with paralysis and atrophy of the deltoid muscle

were, thus, able to develop supplementary movements which greatly improved the function of an otherwise useless extremity. One of them was a 27-year-old male who had a complete paralysis below the 5th thoracic level, due to a severance of the spinal cord, and who also had an irreparable lesion of the posterior cord of the right brachial plexus which resulted in a complete

paralysis of all the extensor muscles of the forearm and hand. He had good function in the flexors of the hand and fingers. The distal tendon of the flexor carpi ulnaris was sutured into the distal tendons of the paralyzed extensor digitorum communis and extensor digiti quinti, the tendon of the flexor carpi radialis was sutured into the distal tendons of the paralyzed extensor pollicis longus and brevis and abductor pollicis, and the tendon of the pronator teres was implanted into the distal tendon of the paralyzed extensor carpi radialis. This procedure gave the patient a useful hand, weakening only slightly the flexion movements but producing enough extension to allow him to write, hold objects in his hand and use them in an adequate manner (Fig. 4).

Physiotherapy is of the utmost importance in the care of the involved extremity, with or without surgical repair of the lesion. Its aim is to prevent the weight of the paralyzed portion of the extremity from overstretching the paralyzed muscles and nerves, to improve the tone of the skin and muscles, to keep the joints mobile and prevent ankylosis and deformities, and to help motion by substituting the use of normal muscles for movements usually performed with the paralyzed muscles (Fig. 5). These treatments consist of light massage and passive motions first, and later, when recovery takes place, of more extensive massage, passive and active exercises. A splint should be worn as long as overstretching or contractures of muscles is not overcome by either recovery of function in the paralyzed muscles or the development of adequate supplementary movements.

The results of the surgical treatment of brachial plexus lesions are, on the whole, not as good as those of peripheral nerves. The distance between the site of the lesion and the muscles and skin involved makes nerve regeneration a slow and prolonged process. Therefore, the end-results should not be evaluated finally for several years after repair. It is also obvious that neurolysis and nerve suture performed upon the plexus can not be done as extensively and accurately as upon a single peripheral nerve trunk. However, Foerster,¹ who performed 29 sutures and 17 neurolyses on 39 patients, reported satisfactory results in the majority of them and, in many instances, complete recovery. He reported failures in three cases of suture, and in three other cases he was not able to suture the nerve trunk following too wide a resection of neuromas. Six of our patients, who were injured in civilian life, have had careful and accurate follow-up examinations over a long period of time, and three have had complete functional recovery, one was greatly improved, and two showed little improvement. The majority of the civilian patients in the series came under our care too long after injury, when the effector mechanisms had been totally destroyed by fibrosis and ankylosis. An insufficient length of time has elapsed in many of the patients injured in military service, and the follow-up mechanism is not functioning sufficiently well as yet, to report accurately upon the results of the treatment in these patients. Estimations of the recovery of function in all peripheral nerve surgery must be based upon the recovery of sensation in isolated areas of supply and upon the recovery of movement in muscles whose action cannot be imitated by supplementary movements.

It is our opinion that the best possible results following brachial plexus injuries may be obtained by operation as soon as the acute effects of injury to the soft parts have subsided. During this interval full advantage must be taken of physical therapy. Then, patients with any residual paralysis should be operated upon. Depending upon the character of the lesion found, all scar tissue should be excised, and, if possible, resection of the neuromas and end-to-end suture of the divided nerves should be performed. If end-to-end suture is not possible without undue stretching, there is sufficient experimental evidence to justify the use of fresh homogenous grafts for the bridging of continuity defects. The surgical treatment of complete avulsions of nerve roots is hopeless. In irreparable nerve lesions, tendon shortening and tendon transplantations should be performed.

REFERENCES

- ¹ Foerster, O.: Die Therapie der Schussverletzungen der Peripheren Nerven. Lewandowsky, Hdb. d. Neurologie, Ergänzungsbd. Chap. 3, Berlin, 1929.
- ² Heidrich, L., and Kuettner, H.: Die stumpfen Verletzungen des Plexus Brachialis. Dtsch. Zsch. f. Chir., 23, 586, 1931.
- ³ Perthes, G.: Supravaginale Sehnentransplantation bei irreparabler Radialislahmung. Zbl. f. Chir., 44, 717, 1917.
- ⁴ Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries. P. Hoeber, New York, 1933.
- ⁵ Scaglietti, O.: Über die Operationstechnik der Verletzungen der Wurzeln des Plexus Brachialis durch Schusswaffen. Zbl. f. Neurochir., 7, 129, 1942.
- ⁶ Stookey, B.: Surgical and Mechanical Treatment of Peripheral Nerves. W. B. Saunders, Philadelphia, 1922.
- ⁷ Taylor, A. S.: The Brachial Birth Palsy. In Dean Lewis' Practice of Surgery, Vol. III, Chap. 7, W. F. Prior & Co., Hagerstown, 1929.
- ⁸ Taylor, A. S., and Casamajor, L.: Traumatic Erb's Paralysis in the Adult. ANNALS OF SURGERY, 58, 577, 1913.

DISCUSSION.—DR. BARNES WOODHALL, Durham, N. C.: Doctor Davis has presented one of the most perplexing and difficult problems in peripheral nerve surgery. I have nothing but admiration for the context of his paper, and I should like to make simply a few comments concerning certain studies to be carried out in this field in the near future. I am sure that the members of this Association, so many of whom have been interested in military neurosurgery, will be glad to know that the National Research Council and the Veterans Administration have now embarked upon a long-time study of nerve regeneration in injuries sustained in the recent war. I am particularly happy to announce that Doctor Davis and Doctor Pollock, and others of their groups in Chicago, will participate in this study and head one of the five Study Centers. I am sure that we will not only learn a great deal about this phase of military neurosurgery but that we shall also gain some knowledge that can be applied to the treatment of civilian injuries of a similar character.

SHOULD THE NECK NODES BE DISSECTED IN PATIENTS WITH CARCINOMA OF THE LIP?*

ROY D. McCLURE, M.D., AND CONRAD R. LAM, M.D.

DETROIT, MICHIGAN

FROM THE DIVISION OF GENERAL SURGERY OF THE HENRY FORD HOSPITAL, DETROIT, MICHIGAN

SHOULD THE NECK NODES be dissected as a prophylactic measure, when there is no palpable evidence of malignant involvement? The senior author's early training in Baltimore, at a time when a strong conviction was prevalent, would lead him to answer yes. However, the question is brought up at this time because of an increasing diversity of opinion in the literature and certain facts from our own experience.

To try to get help on this problem from our own perhaps too limited material, we have reviewed the histories of all patients with carcinoma of the lip registered in our Tumor Clinic. As a correlative study, we have also looked-up the patients with squamous cell carcinoma of other parts of the face and scalp. This study was facilitated by our almost perfect follow-up system, which is under the direction of Dr. Arthur B. McGraw.

The Material.—Seventy-nine carcinomas of the lip and 97 squamous cell carcinomas of other parts of the face and head were included in the study, a total of 176 cases. The rarity of carcinoma of the upper lip, and of carcinoma of the lip in the female, was again demonstrated; there was only one clear-cut carcinoma of the upper lip, and only one carcinoma of the lip in a woman. Could rouge or lip stick be a preventive factor? This last fact is more remarkable when it is noted that almost half (42 out of 97 cases) of the lesions elsewhere on the face were in females. The disease is not on the decrease, as will be seen in Table I, which indicates the number of cases seen in five-year periods.

Pathology.—All of the carcinomas of the lip were squamous cell lesions. A few cases indexed as lip lesions were basal cell epitheliomas, but scrutiny showed that they were more properly called carcinomas of the face near the lips. We have assumed that carcinoma of the lips should include only those lesions which have their origin on the vermilion border or at the mucocutaneous junction. Most of the lesions in the series were graded according to the Broder's classification. Thirty were Grade I, 40 were Grade II, two were Grade III, and two were Grade IV. Five were not graded.

Interval before Treatment.—Ten patients had observed the lesions less than 3 months; 10, from 3 to 6 months; 12, from 6 to 12 months; 14, from 1 to 2 years; and 10 for more than 2 years. In 23 patients, a definite history of the interval was not obtained. Fourteen patients had received previous treatment of some sort, including "burning," radiation, excision, and chemo-surgery with zinc chloride (method of Mohs¹).

Methods of Treatment.—In Table II, it will be seen that the treatment of carcinoma of the lip has been chiefly surgical. Radiation in some form was used in a few cases, either as the sole treatment of the primary lesion or as an adjunct to surgery. The cervical nodes were occasionally irradiated,

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

either prophylactically or therapeutically. The operation upon the lip was usually a V-excision, but where the growth was large, the usual plastic procedures were utilized. The neck dissections were limited to the suprahyoid region—the so-called upper neck dissection.

TABLE I
CARCINOMA OF THE LIP

Five-year Periods	No. of Cases
1920-1924.....	4
1925-1929.....	12
1930-1934.....	5
1935-1939.....	14
1940-1944.....	26
1945-.....	18
Total.....	79

TABLE II

Method of Treatment	5-year Cures	3-year Cures	Followed Less than 3 Years but Well	Died of Cancer, or Alive, with Recurrence	Lost or Died of Intercurrent Disease Before 5 Years	Total
Local excision only.....	10	5	18	0	0	33
Excision and radiation.....	5	..	1	..	1	7
Radiation only.....	2	..	1	1	1	5
Excision recurrent tissue.....	3	..	3
Excision and immediate neck node dissection.....	10	3	5	5	..	23
Excision, neck node dissection and radiation.....	1	..	1	3	..	5
Radiation and late dissection neck nodes.....	1	2	..	3
Totals.....	29	8	26 ^a	14	2	79

The results of the several forms of treatment are tabulated in Table II. Most of the categories of treatment contain too few cases to make it sensible to compute percentages of five-year cures. Nevertheless, it may be stated that there have been no deaths from cancer in those cases selected for treatment by excision only. There were 15 five-year cures and an additional five patients who were well at least three years after the simple operation. There were eight cancer deaths among 28 patients who had excision plus neck node dissection. It should be noted that at least one of the patients who had a late neck node dissection after the primary lesion was treated elsewhere was a five-year cure.

Thirty-one patients had lymph node dissections, and the results in this group are shown in Table III. The nodes were microscopically-positive in only 7 of the 27 cases in which the procedure was done at approximately the same time as the primary operation. Apparently, the operation was unnecessary in the 20 patients in whom the nodes were negative. It is notable that four of these patients subsequently died of carcinoma, hence, the operation does not appear to give a high degree of protection. One of these four patients died of generalized abdominal metastases, without evidence of recurrence in the lip or neck.

It happens that there were no operative deaths among the 31 neck dissections for carcinoma of the lip, but the only time the procedure was carried out for carcinoma of the cheek, an operative death resulted. The cause of death was asphyxia from laryngeal edema and hemorrhage. Incidentally, the

nodes which were removed at the unfortunate operation were microscopically-negative for malignancy. Others have reported alarming mortality rates, such as 11.4 per cent,² and 6.9 per cent.³ On the other hand, there is a series reported in which there was only one death in 549 operations—a remarkable record.⁴

TABLE 111

	Total	Lived	Died Ca.
Immediate dissections:			
Nodes negative.....	20	16	4
Nodes positive..	7	3*	4
Late dissections:			
Nodes positive.....	4	1	3
Totals.....	31	20	11

* One 20-year cure; one 3-year; and one 1-year.

Only three patients are alive who had positive nodes removed. One of these is a five-year cure. He is well 20 years after operation. However, this procedure was not done as a purely prophylactic measure, since the history states that the nodes were palpable and carcinoma was suspected. The operating surgeon states that it was his policy, at the time, not to remove the nodes unless he thought they were involved. There was a three-months delay between the primary operation and the neck node dissection in the patient with the three-year cure. We have been unable to establish, with certainty, whether the surgeon believed these nodes to be malignant before operation. In the case of the patient who has been followed for one year, the nodes were palpable at the time of operation. The lip lesion was large, measuring 3 cm. x 4 cm.—a neglected tumor.

A review of the literature on the subject reveals a divergence of opinion regarding the advisability of routine node dissection. Three years ago, in a paper read before the Southern Surgical Association, Brown and McDowell,⁵ of St. Louis, stated: "It is thought that the rule should be to undertake dissections in patients with primary carcinoma of the lip or mouth. Deviations of care of individual patients should be away from this rule rather than making it a last resort." This seems to be the attitude of the Mayo Clinic, since New⁶ said: "If definite epithelioma of the lower lip can be determined clinically, I feel that it is better to perform a wide V-shaped excision, which should be followed by removal of the lymph nodes of the neck."

Holding opposing views are such writers as Martin⁷ of the group at Memorial Hospital in New York. He stated: "We do not agree with the principle of giving prophylactic treatment to the neck either by surgery or radiation in the absence of palpably involved nodes." A recent study of 56 five-year cures, by Whitcomb,⁸ of Philadelphia, caused him to remark: "Prophylactic treatment of the lymphatics of the neck by surgery or roentgenotherapy is not necessary because most cancers of the lip do not develop metastatic nodes. Follow-up examination of the neck is the ideal form of treatment." Taylor and Nathanson,⁹ of the Huntington Memorial Hospital, operated by the Cancer Commission of Harvard University, studied 616 cases, of which 411 patients had neck dissections. They concluded: "In cases without palpable lymph nodes or with lymph nodes less than 1 cm. in size,

provided this group of cases can be followed carefully, there does not seem to be sufficient likelihood of the development of cervical metastasis to warrant routine dissection."

The results reported by some centers using only radiation are impressive. For example, Schreiner and Christy¹⁰ has a 93.9 per cent cure-rate among the determinate cases in 334 patients in whom there were no palpable nodes, and 85 per cent-rate where there were nodes, some of which were thought to be malignant. Radiation treatment is preferred at the New Haven Hospital, according to a report by Lawrence and Oughterson.¹¹ Lymph nodes are dissected only if they are palpable.

It is frequently stated that if one routinely removes the axillary nodes in carcinoma of the breast, one should be consistent and remove the cervical nodes in carcinoma of the lip. However, it is not unlikely that carcinoma of the lip is more like carcinoma of other exposed parts of the face (nose, chin, cheek, *etc.*) than it is like carcinoma of the breast. In our series of 97 squamous cell carcinomas of these parts of the face, a strictly prophylactic dissection was done in only one case, and that patient died an operative death (edema of the larynx). The results of conservatism in the other cases were excellent, since 90 per cent of the cases followed five years were well, and 96 per cent of those followed three years were well. Only the long-standing, neglected cases were not cured by adequate excision of the primary tumor.

In conclusion, we will state that we do not claim to have the final answer to the question propounded in the title to this paper. However, as a result of this study, we have adopted the policy, for the time being, that it is unnecessary to carry out neck node dissections in patients with small, early carcinomas of the lip, if there is no palpable evidence of node involvement. However, such patients will be followed carefully, the neck being examined every month for one year, and every two months for the second year. If a metastatic node appears, a dissection will be undertaken.

REFERENCES

- ¹ Mohs, F. E.: Chemosurgical Treatment of Cancer of the Lip. *Arch Surg.*, **48**, 478, June, 1944.
- ² Kennedy, R. H.: Epithelioma of the Lip: With Particular Reference to Lymph Node Metastasis. *ANNALS OF SURGERY*, **99**, 81, 1934.
- ³ Eckert, C. T., and Petry, J. L.: Carcinoma of the Lip. *Surg. Clin. N. A.*, **1064**, October, 1944.
- ⁴ Figi, F. A.: Epithelioma of the Lower Lip. *Surg., Gynec. & Obst.*, **59**, 810, 1934.
- ⁵ Brown, J. B., and McDowell, Frank: Treatment of Metastatic Carcinoma of the Neck. *ANNALS OF SURGERY*, **119**, 543, 1944.
- ⁶ New, G. B.: Malignant Disease of the Mouth and Accessory Structures. *Am. J. Surg.*, **30**, 46, 1933.
- ⁷ Martin, H. E.: Treatment of Cancer of the Lip. *Am. J. Surg.*, **30**, 215, 1935.
- ⁸ Whitcomb, C. A.: Cancer of the Lip: A Study of 56 Five-year Cures. *Am. J. Surg.*, **63**, 304, 1944.
- ⁹ Taylor, G. W., and Nathanson, I. T.: Evaluation of Neck Dissection in Carcinoma of the Lip. *Surg., Gynec. & Obst.*, **69**, 484, 1939.
- ¹⁰ Schreiner, B. F., and Christy, C. J.: Results of Irradiation Treatment of Cancer of the Lip: Analysis of 636 Cases from 1926-1936. *Radiology*, **39**, 293, 1942.
- ¹¹ Lawrence, E. A., and Oughterson, A. W.: Carcinoma of the Lip at the New Haven Hospital, 1921 to 1940. *Conn. State M. Soc. J.*, **8**, 353, 1944.

THE PRESENT STATUS OF THE LEG LENGTH DISCREPANCY PROBLEM*

J. WARREN WHITE, M.D.

GREENVILLE, SOUTH CAROLINA

AS THE TITLE INDICATES the purpose of this discussion is to call attention primarily to what can be done about the short leg rather than to go into the details and complications of various technics.

As our surgical ability improves we find we can do such impossible things as were mentioned in Biblical times. "By thought alone we cannot add a cubit to our stature," is a quotation from the Sermon on the Mount. Yet we can, by painstaking effort, literally and figuratively, by the patient and the surgeon, respectively, increase our height a few inches.

In the first place as we appreciate the natural adjustments that our spine, pelvis, and lower extremity can make with impunity if one leg is shorter than the other, the indication for surgical interference is occurring less and less frequently. As further progress in methods of nonsurgical growth stimulation and retardation are discovered, even less surgery will be required in the solution of this problem where organic discrepancies exist during the growing period.

Of the major deformities of the body, perhaps the short leg as an entity has received less space in the literature than any of the others. The explanation of this probably lies in the fact that until the growth arrest conception was originated by Phemister, both the leg shortening and the leg lengthening elective procedures were of sufficient severity and carried with them enough risk to discourage their routine performance. Now, with the growth arrest technic, if the afflicted child is seen early enough and if the deformity is not too severe, leg equalization can be approximated, with a relatively minor operation properly timed, at growth maturity.

More importance, however, the writer feels, has been placed on the effects of moderate leg length discrepancy than is justified, particularly as regards back pain and the development of scoliosis. A limp is altogether too frequently attributed to a discrepancy when it really is produced by an unappreciated hip deformity or a muscle function impairment rather than an actual difference in length.

Many individuals with as much as two inches, or even more, discrepancy in leg length can walk without a limp, while others with no discrepancy at all, but with some condition such as a mild spastic hemiplegia or even an old-time "sciatic scoliosis," now known better as one of the discogenetic syndromes, walk with a bad limp, too frequently attributed to a short leg. We usually are fooling ourselves when we employ lifts on heels for mild or fancied

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

shortening of a leg in a patient with low back pain. They do no harm, however, and often help as a placebo while trying to work out a more rational diagnosis and program of therapy. A great many of us in this audience have a quarter of an inch or more shortening without our being cognizant of it.

In discussing the short leg or the long leg, it is, of course, assumed that all organic or functional deformities have been corrected or at least taken into consideration in deciding a course of action. For example, an adducted ankylosed hip ordinarily should be corrected or accepted for other solution if correction is deemed inexpedient. Likewise, a painless freely movable hip in an adult with two or more inches shortening possibly from a fracture may be better off with a leg equalization procedure than the open reduction ordinarily required. In fixed pelvic obliquities due to a scoliosis such as occurs in severe polio problems, a shortening procedure will frequently be the solution of choice rather than the correction of the more difficult, and not infrequently inoperable, spinal deformity. We must also remember that an ankylosed hip in good position is usually accompanied by a better result than the average arthroplasty.

A technic for measuring leg length discrepancies as accurately as possible should be developed by all surgeons carrying on this work. There is so much chance for error in the conventional tape line measurement from the anterior superior spine to the internal malleolus, that the author feels strongly it should be avoided. A roentgenologic technic has now been used for 12 years, with satisfaction by the author.¹ It consists essentially of taking films of the pelvis with both feet pressed firmly down on a supporting shelf on the table on which roentgenograms are taken. A permanent graphic record of adequate accuracy is thus available for immediate and future reference.

The infrequency of articles appearing in the literature on this general subject until the second decade of the present century shows the formidability with which the surgical procedures were rightfully considered. Both Rizzoli, in Italy, and the elder Sayre, in this country, have been given credit for at least seriously considering the leg length discrepancy problem, but there is considerable justifiable doubt whether in those prelistorian days, *i.e.*, the middle of the 19th century, that they performed the shortening procedures they advocated. Steindler^{1a} gives Rizzoli of Bologna, Italy, undocumented credit for carrying out the idea in 1847. After Codavilla's^{1b} article, in 1905, on leg lengthening, Magnuson's contribution,^{1c} in 1908, was the only one in American literature before 1910. Putti's paper,^{1d} in 1921, laid the groundwork for Abbott's² important contribution six years later, in 1927. Putti, in his 1921 paper, substantiates this statement of Steindler but gives no date and urges anatomic lengthening procedures as more befitting improved surgical technic. Codavilla, appropriately from the Institute Rizzoli, in Bologna, probably read the first paper reporting lengthening procedures in America in 1905, but most of his cases were for malunion of fractures except for one coxa vara. Codavilla is given credit for first using skeletal traction through the os calcis to obtain the required force needed for the correction of these deformities.

The first paper on femoral shortening, in America at least, was written by

Fassett^{2a} in 1918. In it he recommended the step-cutting segment procedure, which the author feels is unjustifiably complicated and which is still being done too often, frequently to the detriment of the patient.

In equalizing leg length differences other than functional adjustments already mentioned, four procedures are possible: First, the long leg can be shortened; second, the short leg can be lengthened; third, in children, the growth of the long leg can be retarded; and, fourth, the growth of the short leg can be stimulated. Generally accepted procedures have been devised for the first three mentioned, but to date no practical method has been contrived to stimulate longitudinal bone growth. It is known that chronic inflammation such as osteomyelitis or even a fracture of the long bones, particularly the femur, will produce enough prolonged hyperemia to materially stimulate growth. In a fracture of a femur in a child, at least half an inch excessive growth can be expected during the year following consolidation, regardless of the amount of actual shortening or deformity that exists:

In most chronic osteomyelitis cases of the lower extremity as well as fractures of the long bones, leg length studies are made at the Shriners Hospital, in Greenville, South Carolina. The greatest difference in leg length attributable to chronic inflammation in observing several hundred cases has been three inches.

The article of Abbott's,² in 1927, was the most detailed scientific treatise on leg lengthening. This was followed by the author's article,³ in 1930, describing a simpler technic, employing the turnbuckle plaster procedure. A fundamentally valuable contribution to the discrepancy problem was that of Phemister's^{3a} on growth arrest, in 1933. Several articles on femoral shortening had appeared before the author's⁴ article, in 1935, but none had advocated the extreme simplicity of the overlap technic before that time.

No paper has yet appeared on the unsolved fourth method of attacking this problem; namely, the stimulation of growth of the short leg. Let us hope that before long some safe, easily and inexpensively-applied procedure may be used to simulate the chronic hyperemia associated with severe trauma and chronic osteomyelitis which has been found to stimulate excessive growth.

The writer, in 1940, did some unpublished animal experimental work on the retardation of growth by heavy roentgen-ray doses, but found, at that time, that the factor of safety between any worth while retardation effect and normal tissue destruction was too limited to make its use justifiable. Barr of Boston, the author understands, is about to publish a report on his experimentation on animals on the possible employment of the roentgen ray for retarding growth. Haas'^{3b} recent contribution on wiring the epiphysis to the diaphysis has been continued by Blount who uses staples instead. The purpose of this work is to use a mechanical means of stopping growth rather than the destruction of the metaphyseal plate and to be able later to release this momentary stoppage and have the growth then continue.

The rationale of Haas' idea, admittedly in the experimental stage, is questioned by the author of this paper, as he feels that the growing force of the

entire metaphyseal plate is stronger than the local restraining action of the staples. We are looking forward to Blount's report on the important work he is carrying on along this line.

In discussing the various merits of the three procedures mentioned above, the author is of the opinion that the growth arrest operation on the distal femur, if the age of the patient permits an adequate correction at maturity, is, by far, the most satisfactory, and if done correctly is attended by fewer complications. For over a 12-year period, the author, assisted by various collaborators—four to be exact (Warner,⁵ Stubbins,⁶ Turkell, and Brewer)—have, with satisfaction, performed routinely a modified Phemister technic which has stopped growth at the distal metaphyseal plate of the femur or the proximal metaphyseal plate of the tibia and fibula, or both, as the occasion requires. He still uses the modified Phemister technic, and in only one instance has a deformity sufficient to require surgical correction been recorded. At the start of this work, in our enthusiasm, 12 cases were arrested prematurely, and a similar procedure had to be performed on the "short" side. By employing the simple arithmetical formula for the correction recommended if the operation is done early, satisfactory correction can be expected.

We still figure on three-eighths-inch correction per year on the distal femur and one-quarter-inch on the tibia and fibula, and that, in girls, growth can be expected to stop at 15 years of age and, in boys, at 16 years. Further investigation regarding full height attainment is being carried out at the present time, and it is felt probably that the bone maturation age is put a little low in boys, and it will probably be raised to 17 years. People just seem to grow faster in the south. (Todd's Atlas^{6a} is employed in figuring growth maturation.)

Except for the fact that it must be limited to children, Phemister's contribution, in 1933, is perhaps the most important of all. The simplicity of the procedure merits high commendation although experience has taught us that an exact operation must be done at the right time, and that records more accurate than most clinics are capable of keeping are essential.

Let us hope that, in the not too distant future, some method not requiring hospitalization will be devised that will accurately and safely stimulate hyperactivity of the metaphyseal plate on the short side and in larger or different doses retard growth on the long side.

Many points, notably the accurate calculation of the time of the expected cessation of growth, are to be worked out in the growth arrest problem. But it is felt that, at least at present, this is the most appropriate method of solving the discrepancy problem where the age of the patient allows it. Roentgenograms are made six months after the operation for the first year, and then annually after that. During the first year little improvement can be expected as the operation itself on the epiphyseal plate tends to stimulate growth in the other epiphyses particularly. After this, regular correction can be expected until growth ceases or unless some growth-disturbing incident intervenes.

While it, admittedly, occurs rarely, the author believes that a bilateral growth arrest is justified on an individual who, according to family tendencies,

will become excessively tall. He has never done this, but Steel, of Pittsburgh, has done the more drastic femoral shortening.

In a few instances multiple procedures are justified, particularly when the remaining period of growth is not sufficient to allow the retardation rate to be effective in time. Here, both femoral and tibial epiphyses either side of the knee can be arrested simultaneously, and in an occasional case even this complicated procedure can be supplemented by a femoral shortening on the same side.

In performing the femoral shortening on children it must be remembered in figuring the amount of shortening that the very operation is a stimulus to growth and not infrequently a full inch extra growth occurs, nullifying possibly to 50 per cent, the result obtained by the shortening. It is advisable, therefore, when shortenings are done during the growing period that growth arrests should be done at the same time.

While it is true the esthetic disadvantage must be seriously considered, it is strongly felt that the added risk of lengthening procedures, except in the case of rare instances, is not worth taking. A large portion of these cases are in polio cases, where usually the lowered center of gravity improves the general stability of the patient.

In closing, it is felt that at this time the following comments are justified:

1. The best way at present to effect equalization in leg length where a patient is in the growing period is to employ single or multiple growth arrests at a time determined by careful calculation.

2. In adults the femoral shortening procedure is justified in selected cases, even in children, if growth arrests are performed, realizing that the operation carries with it very definite hazards.

3. In children and adults leg lengthening procedures are very occasionally justified even by the experienced surgeon, who carefully balances the definite hazard with the indications.

4. It is hoped that, in the not too distant future, a safe practical method for bone growth retardation and stimulation will be formulated.

REFERENCES

- ¹ White, J. Warren: A Practical Graphic Method, *etc.* S. Med. J. 33, No. 9, 946-949, September, 1940.
- ^{1a} Steindler, A.: Orthopedic Operations. Charles C. Thomas, Springfield, Ill., Second Printing, 1943, P. 237.
- ^{1b} Codavilla, A.: On the Means of Lengthening the Lower Limbs, *etc.* Am. Jour. Orthop. Surg., II, 353, April, 1905.
- ^{1c} Magnuson, Paul P.: Lengthening Shortened Bones of the Leg by Operation.
- ^{1d} Putti, V.: The Operative Lengthening of the Femur. J. A. M. A., LXXVII, 934, September 17, 1921.
- ² Abbott, Leroy C.: The Operative Lengthening of the Tibia and the Fibula. J. Bone and Joint Surg., 9, 128, January, 1927.
- ^{2a} Fassett, F. J.: An Inquiry as to the Practicability, *etc.* Am. Jour. Orth. Surg., XVI, 277, September, 1918.
- ³ White, J. Warren: A Simplified Method for Tibial Lengthening. J. Bone and Joint Surg., 12, No. 1, 90-96, January, 1930.
- ^{3a} Phemister, D. B.: Operative Arrestment, *etc.* J. Bone and Joint Surgery, 15, 1, January, 1933.

- ^{3b} Haas, S. L.: Retardation of Bone Growth by Wire Loop. J. Bone & Joint Surg., 27, P. 25, January, 1945.
- ⁴ White, J. Warren: Femoral Shortening for Equalization of Leg Length. J. Bone and Joint Surg., 17, No. 3, 597-604, July, 1935.
- ⁵ White, J. Warren, Warner, W. P. Jr.: Experiences with Metaphyseal Growth Arrests. S. Med. J., 31, No. 4, 411-414, April, 1938.
- ⁶ White, J. Warren, Stubbins, Sam'l G. Jr.: Growth Arrest for Equalizing Leg Lengths. J. A. M. A., 126, 1146-1148, December 30, 1944.
- ^{6a} Todd, T. Wingate: Atlas of Skeletal Maturation. C. V. Mosby Co., St. Louis, 1937.

DISCUSSION.—DR. R. W. JOHNSON, Baltimore, Md.: I have been much interested in Doctor White's paper, because I have always felt he had the last word to say about epiphyseal arrests and shortening. I have fortunately been in the middle ground, as I also admire Roy Abbott's bone lengthening technic, which is a beautiful surgical procedure. I have done both, and at the cost of some labor and much anxiety; I think both have their uses and indications and contraindications. I would *rather* do a shortening or arrest procedure. I think it is easy, and simplest of all in the polio cases when you get the patient young and know what the shortening will be. I think this arrest procedure as performed by Doctor White is best, and in the later cases I think his bone shortening also offers the most simple procedure. But the Abbott operation has a definite place in polio cases where most of the shortening is in the tibia below the knee, where it becomes so much shorter compared to the other leg and to the upper leg as well. These cases with very little tissue in the calf muscles give an opportunity to get lengthening without loss of muscle power, and here, to my mind, leg lengthening is the procedure of choice.

I often lose heart myself in this operation's convalescent period, because it seems a formidable procedure, with turning turnbuckles, *etc.* But when you ask the patients at the end of a year whether they feel it is worth while, they all seem to feel it is. So I think we must balance the procedure against the ultimate results for the patient, and choose carefully between "good leg" shortening and "bad leg" lengthening in the polio cases especially. I do not think a full-muscled leg should ever be lengthened.

DR. BRADLEY L. COLEY, New York City: One measure that can be taken by the profession to prevent unnecessary shortening of a limb is to avoid the use of roentgen-ray therapy for bone cysts and other benign lesions of bone occurring near the epiphysis in children during the period of bone growth. We have seen a number of instances in which such use of roentgen-ray therapy (this was in the early days when it was widely used for a variety of bone lesions, both benign and malignant) was followed by considerable shortening. Unless one follows these children to maturity the importance of this interference with bone growth may be overlooked.

While such an event is no doubt comparatively rare, we have observed three cases of bone cyst, followed for periods of from 12 to 15 years after roentgen therapy, which developed sarcomatous alteration in the involved area. In two of these cases an interscapulothoracic disarticulation had to be performed, and in the third, pulmonary metastasis occurred before a hipjoint disarticulation could be considered.

DR. J. ALBERT KEY, St. Louis, Mo.: I want to ask Doctor White how late in life he does this overlap. It seems to me that if a child is young enough for an overlap an epiphyseal arrest is indicated.

Where shortening is indicated I prefer a step-cut or oblique resection. My last shortening was done with a Blount blade plate. This was in a large girl, age 19, and the operation was quite difficult.

DR. PAUL B. MAGNUSON, Chicago, Ill.: Having become a bureaucrat, I do not know whether I should say anything about surgery, but I did my first leg lengthening operation some 30 years ago, and that patient promptly died. I used very bad judgment in that case; the child was too young and I did not have the proper apparatus. There was too much hemorrhage and shock. After that I confined my attention to leg length-

ening on older patients. I like the step-procedure, but I do not trust to cross strain-bearing screws without any provision for end-bearing thrust to resist the pull of muscles. I do not think one can counteract the pull of the strong muscles in the leg without some form of plug between the ends of the fragments. Doctor White's case in which the screws were broken is an example of what the muscles of the thigh will do if they are allowed to work 24 hours a day without countertraction, and if countertraction is not provided the pull of the muscles will break almost anything which is put in.

I feel that I have done my last leg lengthening operation. It is more sensible to do a growth arrest. I do not think either patient or doctor gets much satisfaction out of one inch difference following operation. I have lengthened legs more than that; in three, toe drop resulted—which finally cleared up—but I do not think the amount of lengthening that can be attained safely pays for the risk and the amount of agony to which the patient is subjected. It is much safer to have a growth arrest or a shortening operation on the other leg. I see no reason for doing a lengthening operation of this sort on growing children. When growth is attained the bones are easier to handle, shock can be more easily dealt with, and one can actually judge whether it will be worth while to level the patient's pelvis by lengthening one leg or shortening the other. I do not think we want to operate unless there is assurance of some permanent value to the patient.

DR. J. WARREN WHITE, Greenville, S. C. (closing): I appreciate these discussions very much, and I think we can answer some of these questions. I am glad to say that Doctor Johnson and Dr. Roy Abbott are still sticking to the leg lengthening procedure more than the rest of us, as I think some of us should still be doing it. I recently asked Doctor Abbott what his opinion was now about this procedure and he said he felt that the lengthening procedure in polio cases should be considered in certain cases. We have also seen the effect of roentgen-ray on a local tumor mass, where growth disturbance has resulted.

Doctor Key is still paying too much attention to the appearance of the roentgenogram. I have had a good many letters from surgeons from various parts of the country, criticizing me for suggesting this shortening procedure, and, in correspondence with them, I have found that they have invariably done more than minimal requirements; the simpler the operation is, the better it is. If we do the step-cutting operation, that means these bone ends have to be accurately shaped so as to make them fit fairly decently. This procedure complicates the operation, and if you know it is going to come out all right, if you do not devote time to that, it is an unnecessary part of the technic and I think it can be safely skipped. In a few years the roentgenograms all look the same.

The oldest overlap procedure I have done is in an individual who went on Saturday night binges too often, and I was tired of repairing pathologic fractures of the femur, as he never seemed to get good solid union. He had lost the other leg, so length compensation could be easily taken care of. I thought that if I reduced his height, he would not be so likely to fracture that bone when he fell. I overlapped it three inches and screwed the bone together. That is five years ago, and I have not heard from him since.

The Blount procedure, which Doctor Key is not so enthusiastic about, I think has a definite place in cases where we want maximum shortening in a large thigh. It is hard to close the wound satisfactorily when the overlap is done in the middle third; there is a mass of muscle difficult to confine in a small space. If a shortening of three inches just below the trochanter is performed, using the blade plate, advantage of the extra space in the upper thigh can be taken, and the wound will come together with much less tension.

In regard to Doctor Magnuson's idea that shortening should not be done in children, I agree with him absolutely, but so often we get these children so late that something more than growth arrest must be done. The growth arrest is not as complicated as Doctor Key seems to think, but it has to be done adequately as well as timed correctly. It is well within the surgical ability of even a surgeon not particularly skilled in these procedures. The solution of the mathematical problem must be done correctly, and should be checked by some other interested surgeon. The final responsibility of these cases should be vested in one member of the clinic staff.

ANALYSIS OF PELVIC OPERATIONS PRECEDING HYSTERECTOMY*

CAUSAL RELATIONSHIP

CURTIS TYRONE, M.D.

NEW ORLEANS, LA.

FROM THE DEPARTMENT OF GYNECOLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE AND
THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, OCHSNER CLINIC, NEW ORLEANS, LA.

THE INCREASE in the number of hysterectomies being performed has become a current source of widespread criticism. It is not my purpose to defend either side of such a controversy but rather to call attention to the number of hysterectomies which have become necessary as a direct result of previous operations upon the pelvic organs. A critical study of 1,048 consecutive cases of hysterectomy performed by me on private patients over a period of 15 years at Touro Infirmary has been made. It was found that previous pelvic operations were directly responsible for the subsequent necessity for removal of the uterus in 436 cases (Table I). This is to say that 41.6 per cent of the total number of hysterectomies performed by me during this period were indicated because previous operations upon the pelvic organs had failed to accomplish their purpose.

It is not my intention to condemn pelvic operations in general. Instead, I would like to call attention to the importance of making a thorough study of the symptoms of these patients before operation and to emphasize the desirability of selecting the surgical procedure which will not only relieve the patient of her symptoms but also obviate the need for subsequent operation as much as possible.

It is, of course, the earnest desire of every surgeon when advising a pelvic operation to relieve the patient of her symptoms but at the same time to preserve the organs of reproduction. However, not one of the 436 patients in this series subsequently became pregnant. Thus, this important function of the uterus was not fulfilled and the uterus remained only to produce a train of symptoms which necessitated a second operation. It would appear, then, that the wiser course in such cases would be removal of the uterus when the patient originally consults the physician regarding such symptoms.

It seems to me that too much emphasis has been placed on the importance of menstruation. It is true that the function of the uterus is childbearing, with menstruation of secondary importance, but too often we encounter women upon whom the surgeon has performed a pelvic operation in an attempt to conserve the uterus, but he has not corrected the principal pathologic condition, and malignant changes have appeared in the uterus several years later. In this

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

series the average time between the previous pelvic operation and subsequent hysterectomy was 4.8 years.

The two complaints most commonly presented by the patients in this series were persistent and increasing pelvic pain and irregular, profuse, intermittent or prolonged vaginal bleeding. Other symptoms complained of less frequently include urinary and rectal discomfort, a sense of pressure in the pelvis and prolapse of the uterus and bladder, leucorrheal and watery vaginal discharge, dyspareunia and sexual disturbances, such as lack of libido and orgasm. These are the same symptoms for which the patient willingly submitted to a previous operation.

TABLE I
PREVIOUS PELVIC OPERATIONS DIRECTLY RESPONSIBLE FOR
SUBSEQUENT HYSTERECTOMY

Indication	Cases	Cases
Salpingectomy.		176
Unilateral	42	
Bilateral	134	
Operations resulting in Stricture of Cervix		125
Amputations	61	
Cauterizations	43	
Conizations	21	
Suspension of Uterus		62
Radium Therapy		37
Benign	30	
Malignant	7	
Vaginal Plastic Operations	...	36
Total..		436

The most frequently performed previous operation was salpingectomy, which was done in 176 of the 436 cases. Despite removal of both fallopian tubes in 134 of these, the patients returned usually with the complaints of pelvic pain and abnormal bleeding, and in some instances malignant changes in some part of the remaining pelvic organs. Would not a more radical procedure in the beginning have been preferable in these cases? It is my opinion that with the improvement in treatment of pelvic infections and the ever increasing knowledge of antibiotics salpingectomy *per se* will become obsolete. In the last ten years I have never removed both of the adnexa uteri without also removing the uterus. There appears to be no justification for ablation of the adnexa only to leave a useless organ such as the uterus which has already become somewhat affected by the previous pathologic process, merely to preserve menstruation, which almost always will become abnormal.

Of the 436 cases complete stricture of the cervix was the direct result of the previous operation in 125 patients. Forty-three of these women had cauterizations of the cervix, 21 conizations and 61 amputations. The indications for the subsequent hysterectomy in these cases were the same as for the previous operations; namely, increasing and irregular pelvic pain and prolonged vaginal bleeding. It is my belief that less radical treatment and more

diligent postoperative care in these cases would have prevented the eventual necessity for excision of the uterus. In the chronically infected cervix it would seem that light office cauterization would not only eliminate the infection but would obviate the need for a future operation. When conization or cauterization is done, constant observation to prevent future strictures is imperative. In the chronically infected, hypertrophied and eroded cervix no form of amputation will completely relieve the patient and at the same time insure against the possibility of future difficulties. The amputation is either too low to do any good or too high. The danger of stricture is obvious; cervical stricture as an etiologic factor in the subsequent development of pelvic endometriosis or uterine malignancy is too well known to require further comment. There is also the possibility of the development of future menstrual disorders and pelvic pain.

Since the uterus is a naturally freely movable organ, too enthusiastic abdominal shortening of the round ligaments or fixation of the uterus to the parietal wall with resulting adhesions only prepares the patient for future difficulties. In the series under discussion there were 62 cases in which a previous suspension operation either failed to relieve the patient of pain and bleeding or later led to such symptoms that hysterectomy eventually became desirable; in 25 of these 62 cases abdominal suspension had failed to correct a prolapsed uterus. In two cases besides the previous suspension operation, intestinal obstruction necessitated a serious operation before the uterus could be removed.

Thirty-seven of the 436 patients required hysterectomy after radium therapy for benign conditions had proved ineffective. In 30 of these the bleeding was not controlled by the application of radium and in an additional seven cases malignancy of the endometrium developed in the uterus several years following radium therapy. These statistics would indicate the necessity for better judgment in the selection of cases for radium therapy.

The statistics obtained from this study are not offered to encourage the promiscuous performance of hysterectomies. However, if a woman presents symptoms requiring surgical intervention in the pelvis, it is the duty of the physician to select the method of treatment which will not only eliminate the patient's complaints but will at the same time prevent the necessity for future operations and eliminate the risk of subsequent development of malignancies when possible. In many cases the only operation which fulfills these requirements is hysterectomy.

SUMMARY

From a critical analysis of 1,048 consecutive cases of hysterectomy performed upon private patients over a period of 15 years it was found that previous pelvic operations were directly responsible for the subsequent necessity for removal of the uterus in 436 (41.6 per cent) cases. None of these patients subsequently became pregnant. The average interval between the previous pelvic operation and hysterectomy was 4.8 years.

The most frequently performed previous pelvic procedure was salpingec-

tomy. Cauterizations, conizations and amputations resulted in complete stricture of the cervix in 125 patients. Suspension of the uterus, done in 62 cases, only prepared the patients for future difficulties. Hysterectomy had to be done in 37 cases of malignancy after radium therapy proved ineffective.

DISCUSSION.—DR. JOHN C. BURCH, Nashville, Tenn.: Doctor Tyrone has brought to our attention a group of cases with which most of us are familiar. We usually refer to them as "do-overs." If the first, or primary operation, had been conducted along physiologic lines there might have been no necessity for the second.

In approaching a pelvic case, the patient must be individualized and her functional needs ascertained. Then the surgeon can intelligently conserve, if possible, those functions which are useful to that particular patient. Our chief error is usually the conservation of a useless function under the misguided label of conservatism. For example, a 40-year-old, para IV, has an ovarian cyst; we remove it and leave the uterus and opposite adnexa. This is conservative treatment. Leaving the uterus leaves the patient subject to all the menstrual difficulties resulting from primary and secondary ovarian failure. An appreciable number of such patients will subsequently develop a menstrual disturbance severe enough to require hysterectomy. An even larger number will have milder symptoms.

Some time ago when studying glandular cystic hyperplasia, we found it could be consistently produced in animals subjected to partial castration. Daily experience confirms the fact that partial castration in the human leads to hyperplasia. Hence, unless the reproductive function must be conserved, it is wise to consider the removal of the uterus also in those women subjected to partial castration. In my opinion, the remaining ovary will function at its normal level. The watchword of the pelvic surgeon might well be the conservation, not of function, but of useful function.



CARCINOMA OF THE BREAST*

A STUDY OF 298 CONSECUTIVE CASES

GEORGE G. FINNEY, M.D., WALTER C. MERKEL, M.D., AND
DONALD B. MILLER, M.D.

BALTIMORE, MARYLAND

THE TREATMENT OF CANCER of the breast has been the subject of careful study for the past 50 years, since Halsted first described his radical operation. Nevertheless, there is still considerable confusion as to whether surgery alone, or a combination of surgery and roentgen therapy will prove more beneficial. Also, the place of androgenic hormones in the treatment of both the primary lesion and metastases is still in the experimental stage. The fact that there is no unanimity of opinion on the proper steps to be taken when a case of cancer of the breast presents itself to the surgeon is well-known. This condition was emphasized by Trimble in his paper published in 1940. He quotes from personal communications from the heads of nine of the important clinics in this country. These replies not only show that there is no one pattern which is universally accepted as the most effective therapy, but also indicates that there is a wide variation in the relative importance attached to radical amputation, the use of pre- and postoperative radiation, and castration, whether accomplished surgically, by roentgen ray, or through the use of hormones.

It should also be added that the operation for the radical removal of the breast for cancer varies a great deal with different surgeons. Some operators will be content with the removal of the breast, together with the pectoral muscles and most of the axillary contents. Many times the dissection of the axillary contents is not carried out with meticulous care, so that every possible shred of tissue that may harbor malignant cells is removed.

Because of the rather confused state of handling cancer of the breast, and the belief that the only way to obtain some firm basis for therapy is by accurate and critical analysis of the results of any particular method of treatment, a study of a consecutive series of cases was undertaken. The series

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

contains all the cases operated upon at the Union Memorial Hospital, in Baltimore, through the 15-year period 1930-1945, by four surgeons; namely, J. M. T. Finney, Sr., William A. Fisher, John M. T. Finney, Jr., and one of the authors (G. G. F.). The first and last named of these surgeons participated for nine and eleven years, respectively, while the other two participated for the full fifteen.

The cases are all private female patients who were referred by their own physicians, or who presented themselves directly to the surgeon. There are no clinic cases in this series. Each case has been proved to have a definite cancer of the breast by pathologic examination, both gross and microscopic, by one

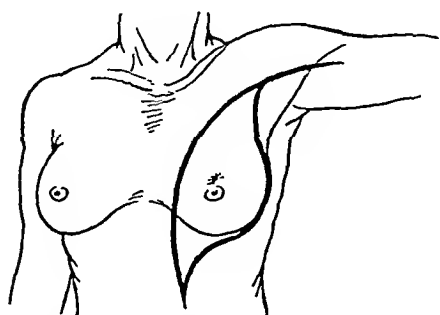


FIG. 1.—Type of incision used in all cases of radical amputation.

of the authors (W. C. M.), who is the Pathologist at the Union Memorial Hospital. No case has been included which comes in a precancerous or equivocal category. Likewise, no case has been omitted because none has been refused the benefit of treatment and so left out of the series. Because of the fact that this study was not undertaken to prove any particular point, but simply to evaluate the results as they were found, the consecutive cases of these four surgeons were studied

because it was felt that this group would represent the same general concept in the treatment of cancer of the breast. This concept is founded on the belief that with our present state of knowledge, it is paramount that the radical removal of the breast be carried out with the strictest attention to detail in every step of the operation, at the earliest possible moment after a definite diagnosis of cancer has been made. The type of operation that has been done in the vast majority of these cases is a modification of the original Halsted operation, and often referred to as the closed plastic operation. An excellent description of this operation was included by Trimble in his paper referred to above, so the details will not be given here. However, it does seem important to point out certain essential steps that should be reemphasized:

1. The cardinal principles of good surgery, namely: the gentle handling of tissue, complete hemostasis, and absolute asepsis, are essential.
2. In making the initial incision, the operator is guided in the amount of skin that is taken solely by the size and location of the tumor, and not with any thought to closure of the wound. The incision is illustrated in Figure 1.
3. Great care is taken to cut the skin flaps thin and evenly, so that there will be a minimum amount of subcutaneous tissue left.
4. After division of the insertion of the pectoralis major and minor muscles, the axillary contents are completely removed by sharp dissection, leaving the axillary vessels absolutely clean, as shown in Figure 2.
5. The complete removal of the entire breast, together with the pectoral

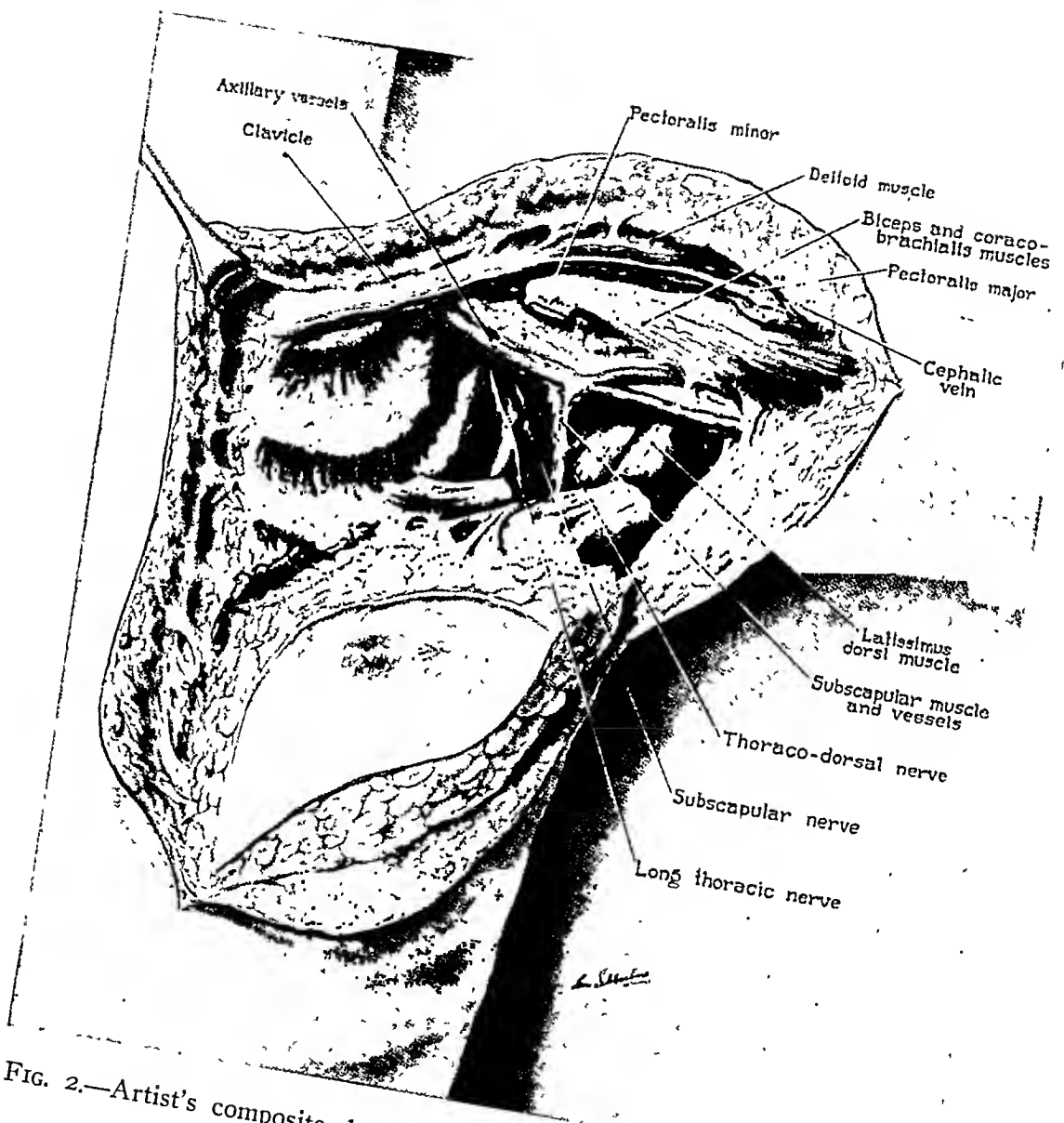


FIG. 2.—Artist's composite drawing of radical amputation showing extent of dissection.

CARCINOMA OF BREAST

muscles and the upper border of the sheath of the rectus muscle in one mass, leaving the chest wall clean.

6. The thorough washing out of the wound with warm normal salt solution before closure, and a thorough check to assure the removal of any extraneous tissue that may have been left and complete hemostasis.

7. In the vast majority of cases, the wound can be closed without undue tension, and grafting is unnecessary. When a graft is necessary, the Ollier-Thiersch type is used and immediately applied.

TABLE I

TOTAL AMOUNT OF ROENTGEN RAY THERAPY

Preoperative treatment.....	7
Postoperative treatment.....	14
Sterilization.....	6
Treatment of late metastases.....	36
Total number of cases treated.....	63

Two of the patients who had preoperative irradiation received a course postoperatively as well. Also two patients who were sterilized by roentgen ray had a postoperative course of treatment to the operative site. There was one patient who was sterilized surgically beside the six shown above.

TABLE II

PATHOLOGIC CLASSIFICATION OF CASES

Group I	Duct cell—with and without chronic cystic mastitis.....	171
Group II	Duct cell—comedo in productive mastitis.....	32
Group III	Duct cell—Paget's disease.....	6
Group IV	Cystadenocarcinoma.....	33
Group V	Adenocarcinoma.....	41
Group VI	Mucoid or colloid carcinomas.....	4
Group VII	Acute carcinosis.....	3
Group VIII	Miscellaneous group.....	8
Total cases.....		298

8. All wounds are drained through a stab-wound laterally, about the level of the midportion of the incision.

As stated above, radical surgery has been the essential form of treatment in this group of cases, although both preoperative and postoperative irradiation has been used in a few of the cases as shown in Table I. Four of the patients who received preoperative irradiation had received this therapy before being referred to the surgeon. The other three were cases who had far advanced lesions and in one of these ulceration of the skin had already taken place by the time the patient sought surgical advice, so a course of irradiation was given before these patients were submitted to surgery. Sterilization as a therapeutic measure has been used in seven patients and it has been recommended

in a number of other instances where the patient declined to submit to it. It is interesting to note that in this series of 298 cases, some 222, or 74 per cent, had already passed the menopause. The use of androgenic hormones in this series has been limited to three cases that had already-developed metastases, and they are under treatment at the present time.

In analyzing any series of data from a group of cases, it is readily seen that it can be broken down in many different ways. In this report an attempt

TABLE III
AGE DISTRIBUTION

	30-40	40-50	50-60	60-70	70-80	80-90
Group I.....	11	43	45	48	18	4
Group II.....	7	7	7	8	3	0
Group III.....	0	1	2	3	0	0
Group IV.....	2	5	10	8	7	1
Group V.....	4	10	10	14	3	0
Group VI.....	1	0	1	2	0	0
Group VII.....	0	0	0	2	1	0
Group VIII.....	1	2	8	2	1	0
Total.....	26	68	77	87	33	5
Unknown—2						

TABLE IV
MARITAL STATUS

	Married	Single
Group I.....	128	43
Group II.....	24	8
Group III.....	4	2
Group IV.....	29	4
Group V.....	35	6
Group VI.....	1	3
Group VII.....	2	1
Group VIII.....	6	2
Total.....	229	69

TABLE V
TIME-LAPSE FROM DISCOVERY TO TREATMENT

2 weeks.....69	1 year.....31	5 years..... 4	15 years..... 2
1 month.....44	2 years.....24	6 years..... 3	16 years..... 1
3 months.....55	3 years..... 9	8 years..... 1	17 years..... 1
6 months.....43	4 years..... 2	10 years..... 2	20 years..... 1
Unknown—6			

will be made to submit tables that will show as clearly and accurately as possible the most important features. Of these 298 cases, it has been possible to get accurate follow-up data on 280, or 94 per cent. There were three patients who died following operation before they left the hospital, and are, therefore, considered operative deaths. This gives an operative mortality of approximately 1 per cent.

It was felt that a careful classification from the pathologic standpoint would be very interesting and important, particularly if any correlation

CARCINOMA OF BREAST

between the different groups and ultimate results developed. Table II gives the pathologic classification of all the cases studied. Group I, of course, contains the largest number, and it was interesting to note that at least 73 cases of the total showed definite chronic cystic mastitis. In Group IV there were included all those cases where the tumor developed from intraductal papillomas, from the epithelial lining of cysts, and also from sweat glands. In Group V, there were those tumors that developed from fibroadenomas, as well as the acinar type. In Group VIII were gathered all those tumors that

TABLE VI
BREAST INVOLVED

	Left	Right
Group I.....	95	82
Group II.....	21	11
Group III.....	4	2
Group IV.....	21	12
Group V.....	24	17
Group VI.....	2	2
Group VII.....	1	2
Group VIII.....	7	1
Total.....	175	129
Bilateral—6		

TABLE VII
LOCATION OF TUMOR

	Upper Outer Quadrant	Upper Inner Quadrant	Lower Outer Quadrant	Lower Inner Quadrant	Upper Half	Lower Half	Outer Half	Central	Whole Breast
Group I	87	15	19	11	14	6	4	16	2
Group II	17	1	3	3	3	0	2	2	1
Group III	1	0	0	0	0	0	0	4	0
Group IV	17	4	2	1	3	1	3	1	0
Group V	18	8	3	1	3	1	4	1	0
Group VI	2	0	1	0	0	0	0	0	1
Group VII	1	2	0	0	0	0	0	0	0
Group VIII	1	2	3	0	0	0	0	0	1
Total	144	32	31	16	23	8	13	24	5
Unknown—8									

did not definitely fit in one of the other seven groups. Simply for the purpose of illustrating each group as we have arranged them, we have included as examples the photomicrographs shown here.

Table III shows the age distribution of the cases, and this follows quite closely the pattern shown in many other important series, except for the fact that the peak is reached in the age-group of 60-70 years, rather than the decade of 50-60. In this series there was no patient in the second decade of life, while there were two patients 31 years of age, the youngest recorded. It is interesting to note that 14 of the 30-40 age-group had evidence of microscopic metastases in the axillary nodes at the time of operation, and only

two of these are still alive, one ten years since operation, and the other two. In this age-group, of the 12 who did not show microscopic metastases in the axillary nodes at the time of operation, five have died with metastases, while the remaining seven have been alive and well for an average of seven years, with the longest 14, and the shortest, two years' duration.

Table IV gives the marital status of the patients, and shows that the ratio is about the same as that which has been found in other reported series.

Table V is not only a very interesting one, but it is also quite shocking, when it is realized that 50 patients had known that they had a lump in the breast for at least two years, or more, and an additional 31 had known of the

TABLE VIII

RELATION OF LOCAL RECURRENCE TO GRAFTING AT OPERATION

Number of Thiersch grafts.....	28
Number of local recurrences.....	18
(a) In grafted cases.....	3
(b) In cases not grafted.....	15
(c) In cases with microscopic metastases at time of operation....	10
(d) In cases with no microscopic metastases at time of operation.....	8

presence of a lump for at least a year. There were many different explanations by the patients as to why they had delayed so long before seeking surgical attention, but there were two main reasons that stood out. The first was the fear that the lump in the breast might prove to be serious, and, therefore, the patient confided her trouble to no one. The second was the fact that the patient had consulted her local medical doctor soon after discovery of the tumor, but after being examined, she had been assured that there was no cause to fear any trouble. Consequently, most of these patients had done nothing until the tumor had obviously increased in size, or until the advent of pain, usually of a sharp sticking quality, had caused them to seek relief. There

FIG. 3.—Duct cell carcinoma showing a marked fibrous reaction representative of Group I.

FIG. 4.—Carcinoma of the ducts, comedo type. Note the marked proliferation of epithelium and distention of ducts.

FIG. 5.—Paget's Disease of the nipple with carcinoma, showing the transition from the non-ulcerated epidermis into the eroded part of the growth. The vacuolated Paget's cells can be seen by low magnification.

FIG. 6.—Papillary carcinoma. The wall of the cyst can be seen at the margin of the photograph. This patient had metastasis to the axillary glands.

FIG. 3



FIG. 4



FIG. 5



FIG. 6

were also many women who were lulled into false security, even though they knew they had a lump in the breast, by the fact that for some time they had had no pain or discomfort, and, therefore, felt there was no cause for alarm.

Table VI gives the relative frequency of involvement of each breast, and it also shows that in this series of cases there were six patients who had bilateral cancers. In these patients the time-interval between involvement of

TABLE IX

CONSOLIDATED VITAL STATISTICS OF ALL PATIENTS																	
No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total	
Alive and Well:.....	0	23	21	11	12	16	7	11	7	7	8	6	5	6	10	150	
No. with microscopic metastases at time of operation.....	0	9	4	4	4	4	2	3	3	3	4	0	2	1	2	45	
No. without microscopic metastases at time of operation.....	0	14	17	7	8	12	5	8	4	4	4	6	3	5	8	105	
Died with Metastases:.....	15	25	24	18	10	5	4	3	3	5	0	2	0	1	1	116	
No. with microscopic metastases at time of operation.....	12	18	15	12	5	2	2	0	0	2	0	1	0	1	1	71	
No. without microscopic metastases at time of operation.....	3	7	9	6	5	3	2	3	3	3	0	1	0	0	0	45	
Alive with Metastases:.....	0	2	1	3	1	1	0	1	1			1				11	
No. with microscopic metastases at time of operation.....	0	2	1	0	0	1	0	1	1			1				7	
No. without microscopic metastases at time of operation.....	0	0	0	3	1	0	0	0	0			0				4	
Total number of cases.....																277	

TABLE X

CONSOLIDATED VITAL STATISTICS OF GROUP I																	
No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total	
Alive and Well:.....	0	15	12	6	5	10	1	2	6	5	4	3	0	3	9	81	
No. with microscopic metastases at time of operation.....	0	6	4	3	3	3	0	1	3	2	2	0	0	1	2	30	
No. without microscopic metastases at time of operation.....	0	9	8	3	2	7	1	1	3	3	2	3	0	2	7	51	
Died with Metastases:.....	8	13	18	10	6	3	2	3	1	4	0	1	0	1	1	71	
No. with microscopic metastases at time of operation.....	6	11	12	8	5	2	2	0	0	2	0	1	0	1	1	51	
No. without microscopic metastases at time of operation.....	2	2	6	2	1	1	0	3	1	2	0	0	0	0	0	20	
Alive with Metastases:.....	0	2	1	2	0	1	0	1								7	
No. with microscopic metastases at time of operation.....	0	2	1	0	0	1	0	1								5	
No. without microscopic metastases at time of operation.....	0	0	0	2	0	0	0	0								2	
Unknown.....	10																
Operative mortality.....	2																

the first breast and the second one was eight months, one year, two years, three years, ten years, and 16 years, respectively.

The pattern of the location of the tumor in the breast is shown in Table VII. In this group of cases, as in many other reported series, the predilection of the upper outer quadrant of the breast as the site of involvement is most striking. In fact, this area contained nearly half of the tumors in the entire series.

CARCINOMA OF BREAST

Let us now turn to the results that we have found in studying this consecutive series of cases. As has been stated above, we have been able to obtain accurate follow-up data on 280 of the original group of 298. The majority of the 18 that could not be traced had come for operation from other cities and contact with them has been lost. It does not seem fair to presume that all of this group have died. It is more likely that they would fit

TABLE XI

CONSOLIDATED VITAL STATISTICS OF GROUP II																	
No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total	
Alive and Well:.....	0	2	2	0	1	3	2	2	0	1	0	1	0	1	0	15	
No. with microscopic metastases at time of operation.....	0	0	0	0	0	1	2	0	0	1	0	0	0	0	0	4	
No. without microscopic metastases at time of operation.....	0	2	2	0	1	2	0	2	0	0	0	1	0	1	0	11	
Died with Metastases:.....	3	4	2	1	0	2	0	0	1	0	0	0	0	0	0	13	
No. with microscopic metastases at time of operation.....	3	3	1	1		0			0							8	
No. without microscopic metastases at time of operation.....	0	1	1	0		2			1							5	
Alive with Metastases:.....									1			1				2	
No. with microscopic metastases at time of operation.....									1			1				2	
No. without microscopic metastases at time of operation.....									0			0				0	
Unknown.....	2																
Operative mortality.....	0																

TABLE XII

CONSOLIDATED VITAL STATISTICS OF GROUP IV																	
No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total	
Alive and Well:.....	0	2	3	4	0	2	2	2	0	1	1	1	2	0	0	20	
No. with microscopic metastases at time of operation.....	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	2	
No. without microscopic metastases at time of operation.....	0	2	3	4	0	2	2	1	0	1	0	1	2	0	0	18	
Died with Metastases:.....	0	4	1	3	1	0	0	0	1	1	0	0	0	0	0	11	
No. with microscopic metastases at time of operation.....	0	3	0	1	0				0	0						4	
No. without microscopic metastases at time of operation.....	0	1	1	2	1				1	1						7	
Unknown.....	2																
Operative mortality.....	0																

into the same general pattern shown by the series as a whole. However this may be, the results of the 277 followed are shown in the following Tables. It has been thought by some surgeons that the incidence of local recurrence following radical mastectomy is usually higher when skin grafting is not made a routine part of the operative procedure. In Table VIII it will be seen that in this series of cases Thiersch grafts were found necessary in 28 cases. In the 280 cases that have been followed there were 18 local recurrences, which is an incidence of approximately 6 per cent. There were three local recurrences in the grafted cases, or an incidence of a little more than 10 per cent,

while there were 15 recurrences in the cases that were closed, or a little less than 6 per cent. It seems that the most important step in preventing local recurrence is the removal of an adequate amount of skin. This, however, does not imply that the application of a graft will be necessary for proper closure.

Table IX is perhaps the most interesting and instructive one of this series. Here the results have been broken down into the three main categories of *Alive and Well*, *Died with Metastases*, and *Alive with Metastases*, for each

TABLE XIII

CONSOLIDATED STATISTICS OF GROUP V

No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Alive and Well:.....	0	3	4	1	5	1	2	2	1	0	2	1	1	1	1	25
No. with microscopic metastases at time of operation.....	0	2	0	1	2	0	0	0	0	0	1	0	1	0	0	7
No. without microscopic metastases at time of operation ..	0	1	4	0	3	1	2	2	1	0	1	1	0	1	1	18
Died with Metastases:	2	3	2	2	2	0	0	0	0	0	0	0	0	0	0	11
No. with microscopic metastases at time of operation.....	1	1	1	1	0											1
No. without microscopic metastases at time of operation ..	1	2	1	1	2											7
Alive with Metastases: ..				1	1											2
No. with microscopic metastases at time of operation . . .				0	0											0
No. without microscopic metastases at time of operation.....				1	1											2
Unknown.....	3															
Operative mortality.....	0															

of the 15 years of the study. At the same time there is shown the number of patients in each of these three categories who either showed the presence of microscopic metastases at the time of operation, or whose nodes were as yet free from metastasis. It can be readily seen that of the 150 patients who have been alive and well for the varying number of years shown, there were 105 who did not have microscopic metastases in the axillary nodes at the time of operation, as compared with only 45 who did. Of the 116 who have already

FIG. 7.—Acinar cell carcinoma. The cells have a tendency to pool, forming pseudo-acinar patterns.

FIG. 8.—Carcinoma arising in a fibroadenoma. The encapsulation of the growth is seen in the corner of the photograph. This patient also had metastasis and most of the growth was well encapsulated.

FIG. 9.—Mucoid carcinoma. Clumps of epithelial cells are suspended in pools of a gelatinous substance.

FIG. 10.—Acute carcinosis. The entire breast is involved, accompanied by a marked lymphocytic reaction. History of rapid enlargement of the breast over a period of six weeks.

FIG. 7



FIG. 8

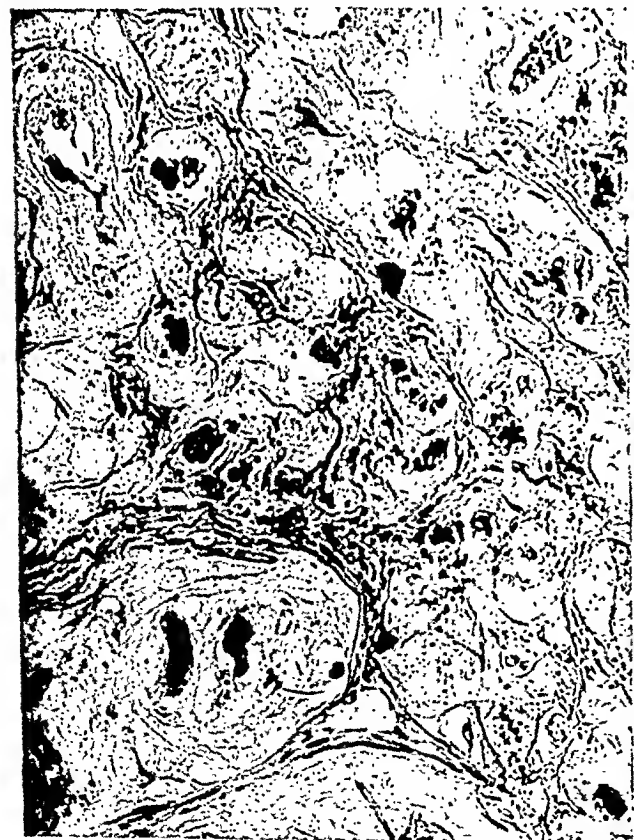
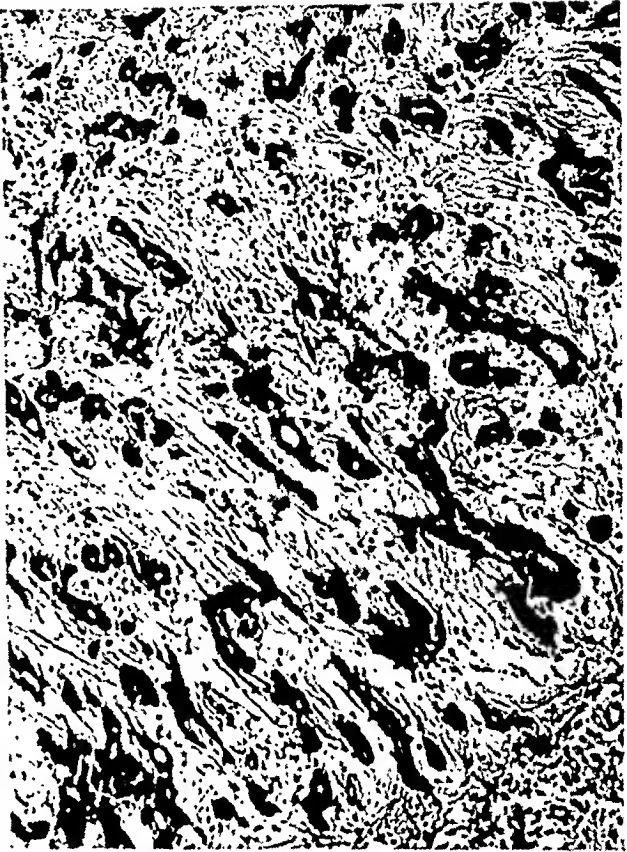


FIG. 9

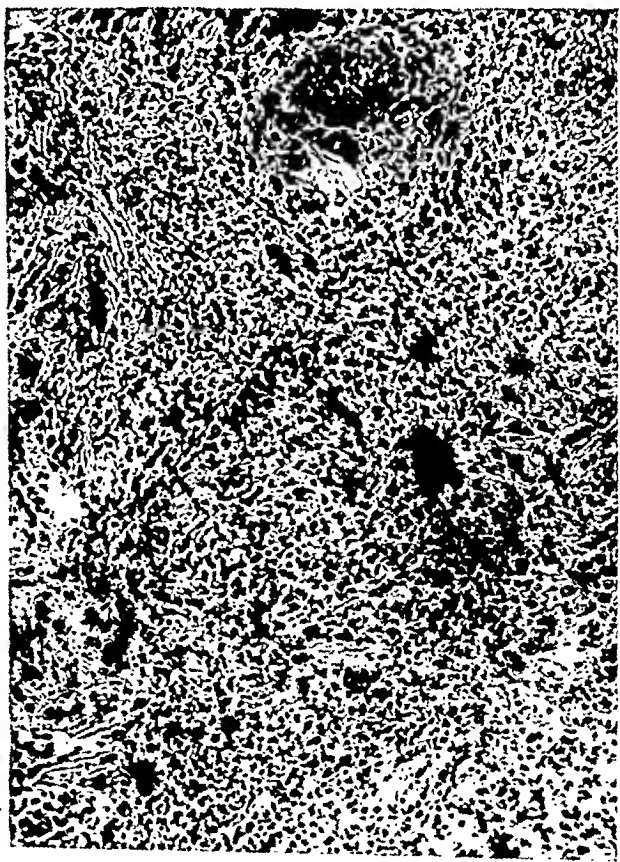


FIG. 10

died with metastases at the end of the varying number of years, as shown in Table IX, 71 had microscopic metastases when radical amputation was done, and 45 did not have any evidence of microscopic metastases at operation but, nevertheless, developed metastases later and died. It should be noted that two patients who had microscopic metastases in their nodes at the time of oper-

TABLE XIV

RESULTS IN ALL CASES

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1.....	277	100	0	15
2.....	262		24	25
3.....	213	77	22	24
4.....	167		15	17
5.....	135	49	14	10
6.....	111		17	5
7.....	89		7	4
8.....	78		12	3
9.....	63		8	3
10.....	52	19	8	5
11.....	39		7	0
12.....	32		7	2
13.....	23		5	0
14.....	18		6	1
15.....	11	4	10	1

TABLE XV

RESULTS IN GROUP I

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1.....	259	100	0	8
2.....	151		17	13
3.....	121	77	13	18
4.....	90		8	10
5.....	72	45	5	6
6.....	61		11	3
7.....	47		1	2
8.....	44		3	3
9.....	38		6	1
10.....	31	19	5	4
11.....	22		4	0
12.....	18		3	1
13.....	14		0	0
14.....	14		5	1
15.....	10	6	9	1

ation are still alive and well after 15 years, while two other such patients had lived for 13 and 14 years, respectively, before dying of metastases. All four of these patients showed tumors of duct cell origin.

Tables X, XI, XII and XIII show results in Groups I, II, IV and V. Because of the small number of cases in the other four groups, these are not included.

CARCINOMA OF BREAST

Table XIV shows quite graphically what has happened to the 277 patients who have been adequately followed. Column 4 entitled "Number not followed beyond this Year," contains all cases who died of some cause other than cancer, of which there was a total of 23. Of these 23 patients, 15 lived one to five years, four lived six to ten years, and the remaining four

TABLE XVI

RESULTS IN GROUP II

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1.....	30	100	0	4
2.....	27		2	2
3.....	21	70	2	1
4.....	17		0	0
5.....	16	52	1	2
6.....	15		3	0
7.....	10		2	0
8.....	8		2	1
9.....	6		1	0
10.....	4	13	1	0
11.....	3		0	0
12.....	3		2	0
13.....	1		0	0
14.....	1		1	0
15.....	0	0	0	0

TABLE XVII

RESULTS IN GROUP IV

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1.....	31	100	0	0
2.....	31		2	4
3.....	25	81	3	1
4.....	21		4	3
5.....	14	45	0	1
6.....	13		2	0
7.....	11		2	0
8.....	9		2	0
9.....	7		0	1
10.....	6	19	1	1
11.....	4		1	0
12.....	3		1	0
13.....	2		2	0
14.....	0		0	0
15.....	0	0	0	0

lived between 11 and 15 years. This column also contains in each year the corresponding number of cases still living who have not been operated upon for a longer period. The column entitled "Died within this Anniversary Year" contains all those cases, but only those cases who died of metastases within each year. It can be seen, therefore, that in order to determine the total

number of patients who have survived at the end of each year, the sum of the "Number not followed beyond this Year" and the number who "Died within this Anniversary Year" is subtracted from the "Number under Observation on this Anniversary." When we have in this way obtained the number of patients who are under observation at the end of each of the 15 years, we can readily determine the per cent who have survived death either from metastases, or any other cause. In Tables XV, XVI, XVII and XVIII it is interesting to see how closely the survival rates parallel each other in spite of the difference in the tumors from the pathologic standpoint.

SUMMARY

1. A consecutive series of 298 cases of cancer of the breast operated upon during the 15-year period 1930-1945 has been studied.

TABLE XVIII
RESULTS IN GROUP V

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1.....	39	100	0	3
2.....	36		3	3
3.....	30	77	4	2
4.....	24		2	2
5.....	20	51	6	2
6.....	12		1	0
7.....	11		2	0
8.....	9		2	0
9.....	7		1	0
10.....	6	15	0	0
11.....	6		2	0
12.....	4		1	0
13.....	3		1	0
14.....	2		1	0
15.....	1	3	1	0

2. A complete follow-up has been obtained in 280 cases.

3. All cases were treated surgically with 281 radical mastectomies and 17 simple mastectomies by four surgeons with an operative mortality of 1 per cent.

4. Only 19 patients received either pre- or postoperative radiation to the tumor site, while seven patients of the premenopausal group were sterilized following radical mastectomy.

5. Hormonal therapy has been used in only three cases, all of whom have metastatic lesions.

6. Of the 150 patients who did not die of cancer metastases, 70 per cent showed no metastatic lesions in their axillary nodes at the time of operation, while 30 per cent showed metastases.

7. In this series the survival rates were 77 per cent after three years, 49 per cent after five years, 19 per cent after ten years, and 4 per cent after 15 years.

8. Radical operation before metastasis has occurred in the axillary nodes gives the best prognosis.

9. A plea is made for the reporting of complete and accurate results of treatment of cancer of the breast so that proper evaluation can lead to better results.

10. Further education is necessary to insure better results in the future.

REFERENCE

- ¹ Trimble, I. R.: Surgery, Gynecology and Obstetrics, 70, 82-92, January, 1940.

CARCINOMA OF THE BREAST: RESULTS OF COMBINED TREATMENT WITH SURGERY AND ROENTGEN RAYS*

SAMUEL F. MARSHALL, M.D.,

DEPARTMENT OF SURGERY

AND

HUGH F. HARE, M.D.,

DEPARTMENT OF RADIOLOGY

THE LAHEY CLINIC

BOSTON, MASSACHUSETTS

SINCE THE INTRODUCTION of radical surgical treatment for cancer of the mammary gland by Halsted and Willy Meyer, radical mastectomy has been the method most commonly employed by the medical profession to treat patients with this type of malignancy. In spite of the fact that radical dissection has approached the acme in the thoroughness of removal of the mammary gland, with its tumor and the surrounding structures of the chest wall and axilla, yet the five-year clinical survival rate has remained relatively stationary and the reported results of treatment of breast carcinoma in the literature has shown a discouraging lack of improvement in the number of patients surviving five years after radical operation.

Carcinoma of the breast in the female, like carcinoma of the female pelvic organs, is one of the most frequent causes of death resulting from malignancy. The United States Bureau of Vital Statistics gives a death rate of 12 per 100,000, and the yearly death rate from this type of malignant disease is approximately 16,000 (Table I).

This high death rate from cancer of the breast each year is a direct challenge to the medical profession and the divergent opinions as to the best method of treating an operable cancer of the breast are evidence of the dissatisfaction with the low survival rate after various methods of treatment. Every effort to increase the salvage of these patients, whether by operation or irradiation, is worth the greatest consideration.

That our experience with postoperative results at the Lahey Clinic has been quite similar to other published results is illustrated by a review of a series of patients operated upon prior to 1936 in this Clinic. Only 38.6 per cent of all patients having radical mastectomy (the majority of this group had no irradiation treatment) survived operation five years or more. These results very closely parallel the figures on results given by Haagensen and Stout⁶ in the treatment of patients with carcinoma of the breast at the Presbyterian Hospital, in New York, over a period of 20 years; they reported a five-year clinical cure of 36.1 per cent after radical mastectomy.

With these facts in mind and since we could apparently not hope, at least in our hands, to improve the survival rate of patients with surgical removal

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

alone, no matter how radically or how skillfully the operation could be done we added to the already radical amputation of the breast, a course of intensive and thorough roentgen therapy applied after operation. Accordingly, beginning in 1935, a uniform method of treatment was outlined and employed whenever possible for all patients with breast carcinoma coming to the Lahey Clinic. This method has been used routinely by us since 1935. It is our purpose in this paper to report the results obtained in this group of patients who have thus been treated, dating from 1935 to 1941, and who have survived a minimum of five years, or longer, without recurrence of tumor. From these results we hoped to draw some conclusions relating to the value or disadvantage of this type of combined treatment. In brief, the treatment has consisted of a Halsted-type of radical amputation of the breast followed by intensive roentgen therapy given in divided doses.

During this period (1935-1941) 283 patients with carcinoma of the breast have received some type of treatment, either radical or simple mastectomy, with irradiation, or some other form of palliative treatment, and of this group, 238 patients have had the complete treatment, that is, radical operation followed by intensive irradiation. Twenty-eight patients have had simple mastectomy, many of whom also had roentgen therapy after operation. It is that group of patients (238) who received the combined method of treatment of radical surgery and irradiation, however, with which we are most concerned in this review.

Although this series of patients is relatively small (238) compared to reports of some larger series of patients, we believe this study to be of value, since these patients have all received the same type of treatment and have been carefully followed and thoroughly studied; and from these data we believe we are justified in attempting to draw some conclusions regarding the efficacy of this combined treatment.

Since 1942 a much larger group of patients has been similarly treated but these patients have been treated too recently to report five-year survival.

In this series we have not attempted to confine our treatment to a selective group of cases that would present a more favorable prognosis but have employed radical operation in all cases in which the cancer was still confined to the breast and to the corresponding axilla. In fact, subsequent pathologic examination of axillary nodes was positive for axillary extension in 62 per cent of the cases. The only contraindication to radical surgery was evidence of distant metastatic spread, involvement of the pleura, of the lungs, bones, or extension to the supraclavicular region.

In general, the radical operative procedure employed has been the method advocated by Halsted, with minor modifications. It has consisted of removal in one block of the breast with its overlying skin, together with excision of the pectoralis major and minor muscles and thorough dissection of axillary contents and fatty and fibrous tissue of the chest wall, including a considerable portion of fascia covering the rectus muscle.

Many types of incisions have been employed by various surgeons; all have

proved useful and each is probably advantageous in the hands of the particular surgeon who is accustomed to his own type of radical mastectomy. The type of incision employed depends to a large measure upon the location of the tumor in the breast. We have used the incision that Halsted later adopted instead of the incision extending out upon the arm which he first described in his earliest report on radical removal of the breast.

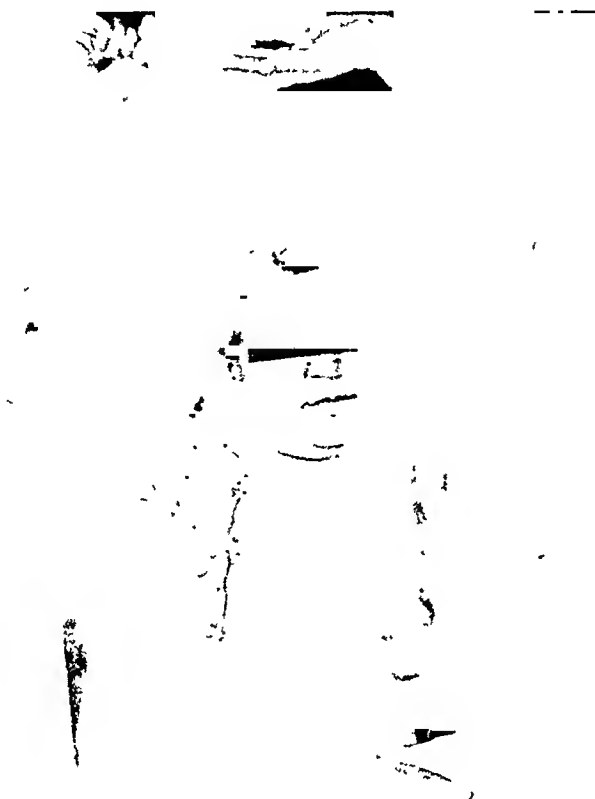


FIG. 1.—Operative wound ten days after radical mastectomy. Incision consists of encircling incision, with incision extended vertically above and below the breast. Note extent of range of motion and primary wound healing ten days after operation. Deep radiation therapy can be started immediately at this stage.

This incision consists of a circular incision about the breast with a vertical incision extending above and below the breast, which, in the majority of cases, permits complete access to the contents of the axilla and chest wall.

The extension of the incision on the arm is unnecessary for exposure of the axillary contents and is likely to result in a contracted scar in the axilla, which may greatly limit return of arm motion. Stewart's simple transverse incision is often useful, and permits sufficient exposure of axillary contents and

allows an easy plastic closure of the wound. It is particularly valuable for tumors located in the extreme lateral border of the breast. Greenough's arrow-head incision permits an excellent approach to the axilla in those tumors which arise high in an axillary extension of the breast, where it may be used most advantageously. We have intentionally limited the extent of the skin excised, removing the skin over the breast and placing the line of skin incision about 5 to 6 cm. from the border of the tumor. This has been done in an effort to obtain a primary plastic closure of skin over the chest wall in order to obtain early healing so that irradiation treatment could be started immediately after radical operation (Fig. 1). Roentgen therapy is started as early as possible, in most cases within eight or ten days after operation. We have thought that wide excision of skin would involve closure of the defect with immediate Thiersch graft, which would greatly prolong healing and seriously delay the institution of radiation therapy.

There are few cases, indeed, in which radical mastectomy cannot be done with a great margin of safety. In this group there was only one postoperative death, which resulted from a coronary occlusion. Following radical mastectomy, these patients are allowed up in a chair on the second or third day. They are encouraged to exercise the arm early and before radiation treatment is started almost all have complete range of motion.

Simple mastectomy has been employed in 28 patients, and only in those patients whose constitutional condition would not permit a radical surgical procedure; in some it was used to remove a large ulcerating lesion or as a palliative procedure in advanced malignancy. Of this group of 28 patients only three have survived five years, and this is to be expected since this operation, in main, was employed palliatively in advanced cancer. In view of the fact that a fairly large group of patients (37 per cent in this report) with axillary involvement can be salvaged by radical mastectomy, there is no logical reason to employ simple mastectomy as a method of routine treatment, as is advocated by many surgeons, and such a method of treatment is to be heartily condemned. Particularly is this true with early carcinoma of the breast, as it is at this time that carcinoma should be treated most vigorously and radical operation has the greatest opportunity to accomplish a cure.

It is unnecessary to state that employment of postoperative roentgen therapy does not represent a new method of treatment as the literature^{12, 13} contains many reports of groups of patients treated with roentgen rays post-operatively, but with few exceptions the roentgen dosage has been small, or has been unrecorded, and seldom has there been reported a series of cases in which a uniform method of such combined treatment has been employed.

IRRADIATION TREATMENT

In 1935, when high voltage shock-proof roentgen-ray equipment became available, it was our opinion that the value of postoperative radiation for carcinoma of the breast was a debatable question. The seriousness of the disease in question, the need of more vigorous treatment and the frequency

of recurrence of the disease made it seem feasible to outline a course of treatment to be given as soon after operation as was possible and to run a series of cases in which operation and radiation would be on a routine basis. The surgical plan which was carried out on this series has been given. Radiation treatment was started within ten days to two weeks following the operation, when we deemed the healing of the wound was satisfactory. Treatment was delivered to the scar, axillary and supraclavicular regions. In all cases a uniform plan of treatment was carried out, using the following factors: 200 k.v.p., 1 mm. copper filtration, distance 50 cm., portal size 15 cm. round cone, daily dose 300 r. As the initial dose 300 r was given to each port treating one portal daily for three days. Following this, each portal was treated daily with 100 r, until 2,400 r had been delivered to each of three portals for an over-all dose of 7,200 r, all measurements taken in air. By giving this postoperative radiation in this manner, there was no material interference with wound healing. There was only a moderate skin reaction to the roentgen-rays, and there were no resulting pulmonary changes, such as radiation pneumonitis. The erythema and desquamation which do occur following this form of treatment are limited to the axilla and scar regions, reach a peak between 15 and 21 days, and the erythema gradually fades off until the skin is normal except for pigmentation at the end of eight weeks. No local treatment other than vaseline or boric acid ointment is necessary to control the effects of radiation dermatitis. The patient's course should be followed in three weeks after treatment to determine the degree of erythema and any complications which may have arisen from the radiation treatment, and, again, at the eight-week period for a review of the entire problem, at which time fluoroscopy of the chest should be done to rule out radiation pneumonitis.

It is apparent from a study of our results that the combined treatment was not successful in controlling recurrence of the disease in 25 per cent of the cases, even when the disease was clinically limited to the breast region. It was unsuccessful in controlling the disease in 62 per cent of those cases in which the disease had already spread to the axilla before operation. A glance at the location of the metastatic disease, however, indicates that there was very little local recurrence or persistence of the disease unless it had spread to regional lymph nodes prior to treatment.

COMPLICATIONS OF RADIATION TREATMENT

The most frequent complication of radiation treatment is nausea, and often this is associated with vomiting. This complication may usually be avoided by giving a high caloric diet, by delaying treatment for a day or two or by decreasing the daily dose. It was not necessary to decrease the daily dose except in a very few cases.

In all cases there was a moderate skin reaction consisting of erythema and in most cases desquamation of the skin beneath the axilla where the skin from the arm rubs against the skin of the chest wall. In no case was this a serious complication; however, it should always be explained to the patient that this

is going to occur and that proper healing will take place in eight weeks' time. One severe complication which follows radiation treatment over the chest wall is radiation pneumonitis, which has been entirely avoided in this series by treating with small daily doses; with realization that this may occur, it should be pointed out that the differential diagnosis is between true pneumonia, radiation pneumonitis, and secondary malignancy. It is further necessary to emphasize that these changes in the lung should never be treated by further radiation even though it should prove later on to be a recurrence of the disease, especially if the pulmonary changes come within 120 days following treatment.

In radiation pneumonitis, coughing is likely to be severe and may be difficult to control even with large doses of codeine, and in some instances heroin has been used to control the cough. In the cases in which we have seen radiation pneumonitis the effects of the disease gradually disappeared in about 90 days, or less, leaving a residual fibrosis and atelectasis of the lung involved, with disappearance of cough.

PALLIATIVE RADIATION TREATMENT

The radiation treatment for carcinoma of the breast other than for post-operative localized treatment is delivered as a palliative measure for recurrence in the skin, nodes, bone or abdomen. Lesions in the lungs are usually refractory to treatment and lesions involving the cranial vault, unless small and localized, are probably best not treated unless the patient understands that the hair is to be removed as a result of treatment.

The quantity of roentgen-rays necessary to bring about relief of pain from bone lesions is relatively small and should not be given in large enough dosage to produce roentgen sickness or complications of treatment. We use a maximum of 1800 r to each area and never treat a portal larger than a 15 cm. round cone in order to avoid radiation sickness and skin damage. It is generally recognized that if the lesion is hematogenous in type and involving bone, a cure is almost impossible, although there have been several reported cases of patients living for five years, or more.

When the spread of disease is lymphatic and localized to skin a single large dose of roentgen-rays may be used if the lesion is not larger than 2 cm. It must be recognized that spread has likely taken place through other lymphatic channels before treatment is given, and many times it has spread some distance from the first-noted lesion, but it is always advisable to include at least 1 cm. of skin in the field to be irradiated in order to block-off lymphatics, and, thereby, stop further lymphatic spread. It is our custom to shield the remaining skin with 0.5 mm. of lead and treat with a small cone. We use superficial radiation treatment, 90 k.v.p., 20 cm. distance, and give 2,400 r measured in air at one sitting. If the lesion is larger than this, we prefer to use the divided dose technic, using 1,000 r at each treatment, for three treatments. In about ten days following this type of radiation treatment there is moderate radiation reaction, with blistering and crusting of the skin, which

will persist for six to eight weeks, but, in our hands, with this type of treatment the skin usually heals well in eight weeks' time and leaves only a residual, thin, tissue paper-type of scar.

We believe that the irradiation treatment of small recurrent nodules of the skin is preferable to surgical removal, as surgery does not block surrounding lymphatics, and radiation treatment may be given without untoward reaction to the patients on numerous occasions. We have a number of patients, under observation at the present time, with scar metastases, who have been under treatment and followed for as long as three years without evidence of spread of the disease elsewhere.

USE OF ESTROGENIC SUBSTANCES FOR PALLIATION

Recently there has been much interest in the value of the treatment of advanced carcinoma of the breast by estrogenic substances, when these substances are given in relatively large doses.⁵ In some cases this treatment has given remarkable relief of symptoms, such as pain, and has decreased the size of the tumor mass; occasionally, the ulceration has completely disappeared. This is contrary to our understanding of the growth of breast carcinoma, yet it is, in part, fundamentally sound because large quantities of estrogenic substances completely block pituitary secretion of follicular stimulating hormones, commonly known as FSH. Once the pituitary hormones are blocked off, healing of the tumor takes place temporarily but it is only occasionally that relief may be obtained by this method for over a year. There are some observers who feel that carcinomas of the breast become more radio-sensitive during this period that the estrogenic substances are being given.

There is another group of scientists who are giving testosterone propionate to the female in the hope of bringing about relief of symptoms. Again, this may be successful in some cases but in our hands it has not given favorable results.

About a year and a half ago a man, age 60, was admitted to the Clinic following radical mastectomy, with numerous bone metastases. He was given 30 mg. of estrogenic substances daily in the form of stilbestrol, with complete relief of pain and with gradual but complete healing of the bone lesion. Figure 2 shows the bone at the time administration of estrogenic substances was started, and Figure 3 shows the condition of the bone seven months following stilbestrol treatment. In eight months there was a gradual return of symptoms and further treatment by estrogenic substances did not give relief.

PALLIATION BY ROENTGEN STERILIZATION

In 1929, Dresser⁴ reported on the value of roentgen sterilization in the treatment of bony metastases, and presented a case in which treatment had been given three years previously by radiation sterilization, with resultant healing of the bony lesions. This result lasted for a period of seven years. Since that time there have been numerous patients who have received roentgen sterilization in the younger group, who had obtained remarkable relief of pain

and an increase in their number of useful years. There have been more patients treated who did not improve following sterilization than did. In these

FIG. 2

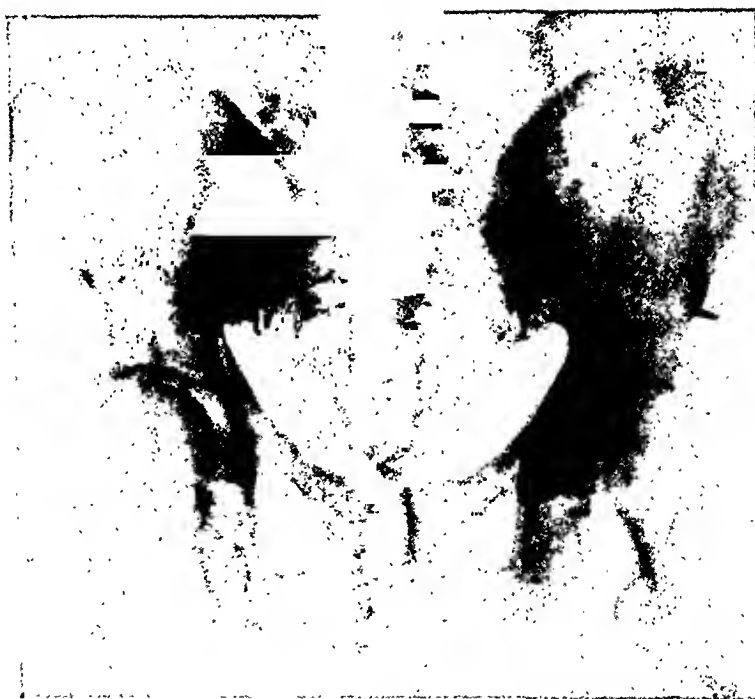


FIG. 3

FIG. 2.—Carcinoma of breast, male. Osteolytic metastases, particularly ischium on left (April 16, 1945).

FIG. 3.—Same case as shown in Figure 2, seven months later, showing repair, with disappearance of ischial lesion.

we add another problem which the patient had to solve; namely, the menopause, which comes at a time when she is mentally upset as a result of the tumor, a complication which has been very difficult to handle in several

instances. It was, therefore, deemed necessary to attempt to analyze the histories of those who did not receive benefit from radiation sterilization, likewise, the histories of those who did receive benefit from sterilization. It became apparent on reviewing these histories, and it has been reported by Sosman,¹⁴ that radiation sterilization was successful only in those cases in which the pain in the metastatic region was increased, and there was associated pain and swelling of the opposite breast at the time of the menstrual period. If these be used as fair criteria for stopping the menstrual period, then a high percentage of patients will receive fair palliation (Figs. 4 and 5).

TABLE I
CARCINOMA OF THE BREAST — MORTALITY,
UNITED STATES BUREAU OF VITAL STATISTICS

	No. of Deaths	Rate per 100,000
1942.....	15,954	11.9
1943.....	16,140	12.0

TABLE II
COMBINED THERAPY, RADICAL MASTECTOMY PLUS POSTOPERATIVE ROENTGEN THERAPY
FIVE-YEAR SURVIVAL RATE—238 PATIENTS

	Number of Patients	5-year Survivals with No Recurrent Tumor	
		Number	Per Cent
No axillary node metastases at operation.....	94	71	75
With axillary node metastases at operation.....	144	53	37
Total.....	238	124	52.1

Adair, *et al.*,² found that roentgen-rays and surgical castration gives improvement in approximately 13 to 15 per cent, and that improvement is temporary and growth is retarded for about two years.

It has been our experience in the treatment of metastatic malignancy secondary to carcinoma of the breast that the patient is usually hopeful until the very end, is remarkably coöperative, and is usually willing to try any type of treatment suggested. It is important, therefore, that we should not give these patients any type of treatment which will make them more uncomfortable.

Each one of these patients in this study has been seen and examined by one or both of the authors in this follow-up, and we believe these statistics are as accurate as can be obtained by direct observation. Of this group of 238 patients who received the complete treatment, 52.1 per cent have survived five years or longer without evidence of recurrence (Table II). When this figure of 52.1 per cent five-year survival is contrasted with our previous experience of 38.6 per cent five-year survival after operation alone, it is evident that there is considerable improvement in the results of treatment, and we believe this must be attributed in a large measure to the added effect of roentgen therapy, as there has been no attempt to select for the combined treatment a group of cases which might offer a more favorable prognosis.

CARCINOMA OF BREAST

This is demonstrated by the fact that in this group of 238 patients, 62 per cent had metastases to axillary nodes at the time of operation (Table III).
Adair,¹ also, has stated that modern irradiation by the divided dose method

FIG. 4



FIG. 5

FIG. 4.—Roentgenogram taken October 6, 1944, showing multiple osteolytic metastases.
FIG. 5.—Same case as shown in Figure 4, two months later, showing healing of metastatic lesions.

after radical mastectomy has definitely increased the survival rate in his cases of cancer of the breast. His figures very closely parallel our experience in this regard; in his series, of 277 patients treated by radical mastectomy followed

by irradiation, the five-year survival rate was 76.8 per cent when lymph nodes were not involved and 41.8 per cent when axillary involvement was present (65.7 per cent of his group had axillary involvement). Adair has employed 1,800 to 2,250 r per portal. Harrington,⁷ of the Mayo Clinic, also reported that the five-year survival rate in a large group of cases, with and without axillary involvement, was improved approximately 5 per cent by the addition of irradiation (Table III).

On the other hand, Haagensen, in reporting the results obtained in a series from the Presbyterian Hospital (640 with radical mastectomy), said that irradiation has not been of demonstrable value in his series. He reported a five-year clinical cure of 36.8 per cent after radical mastectomy alone, and 35.1 per cent when irradiation was used after operation. The roentgen dosage

TABLE 111
RADICAL OPERATION WITH POSTOPERATIVE IRRADIATION
FIVE-YEAR SURVIVAL RATE

	Memorial Hospital Per Cent	Mayo Clinic Per Cent	Lahey Clinic Per Cent
Axilla negative:			
With roentgen therapy.	76.8	75.4	75.0
Without roentgen therapy.....		70.2	
Axilla metastases:			
With roentgen therapy.....	41.8	29.4	37.0
Without roentgen therapy.....		24.3	

employed in this group, however, was considerably smaller than that employed by Adair, or the dosage used in our series, only 800 r per portal in three areas being used. McGraw,¹⁰ in 412 cases from the Henry Ford Hospital, reported a five-year survival rate of 29.6 per cent in 251 patients with axillary involvement, and 64 per cent in 161 patients with negative axillary nodes. He stated that irradiation therapy was used in those patients with axillary metastases. Of 177 patients surviving five years, or longer, 116 were given deep radiation therapy, with 55 per cent having no evidence of recurrent tumor; of 61 not given radiation treatment, 59 per cent are living, and well, without recurrent tumor. He does not state the irradiation dosage used. On the other hand, some very capable observers feel that postoperative irradiation therapy is of doubtful value. Cantril and Buschke³ believe that radiation treatment can slow up growth locally but will have no effect upon the ultimate progress of the disease. They believe that the greatest palliative accomplishment of roentgen therapy is retardation of bone metastases and alleviation of pain. This opinion seems at variance with our results since there appears to be quite definite improvement in our five-year survival rate as well as a decrease in the frequency of local recurrences.

LOCATION OF METASTASES

In studying our group of 238 cases which have been followed by us for over five years, it seems pertinent to analyze the cause of our failures and to study the location of the metastatic nodules, whether the recurrence took place as a result of lymphatic or hematogenous spread. It is quite apparent from our studies that the most common type of spread is through the lymphatics and, yet, once the original lymphatic area is treated by radiation, there is only small likelihood of recurrence or persistence in the area treated.

In this series a total of 114 recurrences was noted in different individuals. Their location is listed in Table IV.

TABLE IV
LOCATION OF RECURRENT MALIGNANCY—238 PATIENTS

	Lahey Clinic		Presbyterian Hospital Per Cent
	Cases	Per Cent	
Spread to opposite breast.....	8	3.3	9.1
Spread to bone.....	23	9.7	17.8
Generalized spread to bone and lymph nodes..	25	10.5	
Recurrence in scar.....	14	5.9	
Recurrence in supraclavicular region.....	4	1.7	13.9
Recurrence in axilla.....	1	0.4	6.6
Recurrence in lung.....	24	10.0	21.6
Recurrence in abdomen and liver.....	7	2.9	9.8
Recurrence in cranium.....	8	3.3	

This shows that a total of 8 per cent of the cases had recurrence of their lesions in the scar area, supraclavicular, and axillary regions, and in this group of cases, 62 per cent showed signs of secondary malignancy to the axilla at the time of operation. This is, indeed, a small group as compared with the recurrences in this area usually noted. It seems necessary, therefore, to treat the scar, supraclavicular and axillary regions following operation especially in those cases in which there is evidence of secondary nodular disease at the time of operation.

Haagensen and Stout⁶ report local recurrence in 22.8 per cent within five years in the operative field on the chest wall and in the homolateral axilla, whereas, with the combined treatment of surgery and radiation we found recurrent tumor in only 8 per cent, which figure includes the supraclavicular region as well. This lack of local skin recurrence appears most significant in our cases especially, in view of the fact that we have been more conservative in the removal of skin over the breast and chest area, in order, as stated before, that primary closure could be done and radiation treatment started immediately after operation. Certainly, it is evident by this conservatism that the frequency of local recurrent growths has not increased, as might be expected from other reports in which wider skin removal was thought absolutely necessary. Lewis and Rienhoff,⁹ in a report from the Johns Hopkins

series, reported local recurrences after Thiersch graft to be 30.1 per cent; after closed plastic to be 39.7 per cent. White¹⁵ is of the opinion that a chest without skin graft is preferable to one with a skin graft and that there is insufficient proof that the Halsted method of wide skin removal with Thiersch graft lowers the incidence of local recurrence as compared to the plastic skin closure of Handley.

Hoopes and McGraw⁸ reported local recurrence to axillary and breast areas in 20 patients out of a total of 91 (22 per cent) upon whom skin graft was done, whereas, in 139 patients with plastic closure there were 22 with recurrence in these areas, an incidence of 16 per cent.

TABLE V
RESULTS OF RADICAL MASTECTOMY AND RADIATION TREATMENT
238 PATIENTS

	Cases	5 yr. Survival without Recurrence		Dead within 5 Years		Died within 2 Years after Operation	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Negative axilla.....	94	71	75.0	23	25.0	10	43.5
Axilla nodes positive.....	144	53	37.0	91	63.0	47	52.0
Total.....	238	124	52.1				

It is also significant to note that a large number of deaths took place within the first two years following treatment. Fifty-seven patients died in the first two years (Table V). This figure represents exactly 50 per cent of the total number dead (114) at the end of the five-year period: ten patients without axillary involvement at the time of operation and 47 patients with positive nodes were dead in the first two years. We could draw no conclusion concerning fertility relative to the combined therapy, yet it is significant, as to the occurrence of the disease at least, that cancer occurred in nulliparous women in 40 per cent of this group. Nathanson¹¹ stated that it is an accepted fact that nulliparous women have a relatively higher incidence of cancer of the breast than those who have borne children, and this high incidence of cancer in nulliparous women in this group is indicative of this fact.

The study in relation to age-groups, likewise, offered no significant data; there were only 28 patients of this group of 238 with the complete treatment who were below the age of 40, and we are unable to say whether the usually reported high early mortality after treatment is at all altered in young women by postoperative radiation or not (Table VI).

The largest group, 189 patients (80 per cent) ranged in age from 41 to 70 years. We did not hesitate to employ radical mastectomy in the older-age group, as indicated by the fact that there were 21 radical mastectomies in patients over 70, and yet in this entire group of 238 patients who had the complete treatment there was but one immediate death following treatment, an operative mortality of 0.42 per cent.

It is difficult in a series as small as the group reported in this paper to draw final and definite conclusions regarding this most important phase of recurrent malignant disease in breast cancer, but it does appear that immediate postoperative radiation therapy, given in adequate dosage, might well influence the occurrence of local recurrent growths, and reduce such local recurrences as well as improve the five-year survival rate. In any case, it is our opinion that there has been improvement in results of treatment of breast cancer by this method and that further information will need to be collected on a larger group of patients treated in a similar manner. We are continuing this method of treatment in the Lahey Clinic and at present have under observation a somewhat larger group of patients who have also had this type of treatment, beginning after 1942. The five-year survival rate is purely a

TABLE VI
AGE INCIDENCE—238 CASES
TREATMENT—RADICAL SURGERY PLUS POSTOPERATIVE IRRADIATION

Age, Years	Cases	
20-30.....	6	} 28 (11.7%)
31-40.....	22	
41-50.....	79	} 189 (80%)
51-60.....	66	
61-70.....	44	
71-80.....	21	

method of measurement of results of treatment and is not the ultimate or final result in any of these cases. What the results of a long range study may be can be estimated only after many years and perhaps after the majority of patients so treated may have died either from recurrent malignant disease or from other causes.

SUMMARY

Radical surgical removal of breast carcinoma followed by intensive irradiation treatment appears to improve statistical results in cancer of the breast and offers the best possibility for prolongation of life. In a series of 238 patients who received this type of treatment, 52 per cent were alive after five years, or longer, without evidence of recurrent tumor.

The incidence of local recurrent tumors is materially reduced, there being only 8 per cent of such recurrences noted in this series.

Radiation therapy, given in large amounts by the divided dose method, has produced no serious complications.

We believe that failure in treatment in many cases results from spread of disease to distant areas prior to institution of treatment.

REFERENCES

¹ Adair, F. E.: The Rôle of Surgery and Irradiation in Cancer of the Breast. J. Am. Med. Assn., 121, 554-559, February 20, 1943.
² Adair, F. E., Treves, Norman, Farrow, J. H., and Scharnagel, I. M.: Clinical Effects of Surgical and X-ray Castration in Mammary Cancer. J. Am. Med. Assn., 128, 161-167, May 19, 1945.

- ³ Cantril, S. T., and Buschke, F.: The Rôle of Roentgen Therapy in Carcinoma of the Breast. *West. J. Surg., Obst. and Gynec.*, 54, 369-370, September, 1946.
- ⁴ Dresser, R.: Irradiation Treatment of Malignancy. *New England J. Med.*, 201, 1285-1287, December 26, 1929.
- ⁵ Farrow, J. H.: The Effect of Sex Hormones on Skeletal Metastases from Breast Cancer. *Surgery*, 16, 141-151, July, 1944.
- ⁶ Haagensen, C. D., and Stout, A. P.: Carcinoma of the Breast. I. Results of Treatment. *ANNALS OF SURGERY*, 116, 801-815, December, 1942.
- ⁷ Harrington, S. W.: Surgical Rates of Radical Mastectomy for Unilateral and Bilateral Carcinoma of the Breast. *Surgery*, 19, 154-166, January, 1946.
- ⁸ Hoopes, B. F., and McGraw, A. B.: The Halsted Radical Mastectomy. *Surgery*, 12, 892-905, December, 1942.
- ⁹ Lewis, Dean. and Rienhoff, W. F., Jr.: A Study of the Results of Operations for the Cure of Cancer of the Breast. *ANNALS OF SURGERY*, 95, 336-400, March, 1932.
- ¹⁰ McGraw, A. B.: Personal communication.
- ¹¹ Nathanson, I. T.: The Relationship of Hormones to Diseases of the Breast. *Surgery*, 16, 108-140, July, 1944.
- ¹² Peters, M. V.: Radiation Therapy of Carcinoma of the Breast. *Canadian Med. Assn. J.*, 51, 335-343, October, 1944.
- ¹³ Petersen, H. G.: Roentgen Treatment of Carcinoma of the Breast. *Acta radiol.*, 25, 1-12, 1944.
- ¹⁴ Sosman: Personal communication.
- ¹⁵ White, W. C.: The Problem of Local Recurrence after Radical Mastectomy for Carcinoma. *Surgery*, 19, 149-153, January, 1946.

TREATMENT OF CANCER OF THE BREAST IN PREMENOPAUSAL PATIENTS WITH RADICAL AMPUTATION AND BILATERAL OOPHORECTOMY*

GUY W. HORSLEY, M.D.

RICHMOND, VA.

FROM THE SURGICAL DEPARTMENT, ST. ELIZABETH'S HOSPITAL, RICHMOND, VIRGINIA

THAT THE OUTLOOK for cure of carcinoma of the breast is more discouraging in young women than in those in the postmenopausal period has been rather generally accepted. Sittenfield¹ states: "Every cancer worker realizes that cancer of the breast in a woman under 40 years of age is a highly malignant disease and notwithstanding the most thorough surgical excision and large doses of radiant energy, the end-results are very grave and disappointing." Ewing² has stated: "Before 30 years of age mammary cancer is extremely fatal, so that some surgeons prefer not to operate during this period."

The relationship of the endocrines to certain types of cancer seems to be definitely established. When, in 1932, Lacassagne³ induced mammary carcinoma in male mice by injections of estrone benzoate it was apparent that an important step forward had been made in the understanding of the causes of mammary cancer. This led to a variety of interesting findings concerning the general effects of the estrogens on neoplasms. Likewise, Huggins⁴ and his coworkers have established in their experimental and clinical work on cancer of the prostate a definite relationship with male sex hormone. Whatever may be the explanation of the benefits of orchiectomy on cancer of the prostate, and they certainly exist in many cases, it would seem that an analogy might apply to bilateral oophorectomy in cancer of the mammary gland.

Shimkin⁵ states: "It was found that mammary tumors occurred more frequently in breeding than in nonbreeding mice. In some strains, the incidence of tumors is proportional to the number of pregnancies undergone by the mice. Loeb⁶ further demonstrated that the incidence of tumors can be radically reduced by ovariectomy, and that the incidence is related to the age of the animal at the time of ovariectomy. Cori,⁷ and W. S. Murray,⁸ substantiated these findings, and the latter succeeded in obtaining mammary tumors in castrated male mice bearing ovarian grafts."

"With the advent of chemically isolated estrogens, numerous investigators reported the appearance of mammary tumors in male mice injected with these compounds. The work was rapidly expanded and elaborated. The most important conclusion was that estrogens would elicit mammary tumors in males of strains in which females developed such tumors spontaneously, and in approximately the same incidence. Males of strains in which the tumor incidence was

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

extremely low did not develop a mammary cancer no matter how strenuously they were treated with estrogens. This would indicate that the strains known to be readily susceptible to cancer of the breast, whether male or female, would develop cancer of the breast by injections of estrogens."

Mammary carcinoma in male mice of susceptible strains has been developed with all the natural and synthetic estrogenic compounds that have been studied. The list includes estradine, estrone, estriol, quilenin and their benzoates, diethylstilbestrol, *etc.* The carcinogenic activity of these substances seemed to be related to the amount of estrogen in physiologic units rather than to chemical structure or other properties of the substance injected. They could be administered subcutaneously, intramuscularly, or orally with the same results, depending on the physiologic activity by the particular route employed. The administration had to be continued for a prolonged period, eight weeks or more, if carcinoma was to be developed at a later period. Compounds having rapid elimination and consequently a shorter period of activity had to be given in larger doses and administered over a longer period than those compounds given as subcutaneously implanted pellets.

The site, the growth, and the histologic appearance of the mammary tumors developed in castrated mice injected with estrogens correspond in every detail with the description of the spontaneous adenocarcinomas in female mice of the same strain.

Using rats of the Long-Evans hooded strain, in which only four fibroadenomas had been seen in 15 years, Nelson⁹ reported the induction of 68 carcinomas of the breast in 103 animals. He gave daily injections of 50 *gamma* of diethylstilbestrol, or subcutaneously implanted pellets of diethylstilbestrol. Metastases developed in 33 rats, which were classified as: duct carcinoma, 13; adenocarcinoma, 8; duct and adenocarcinoma, 13; and carcinoma simplex, 5. He found that both male and female rats were equally susceptible to the induction of tumors. Numerous other workers have repeated the experiments, using the same strain of rats, with essentially the same results.

Geschickter¹⁰ injected a number of castrated rabbits with daily doses of 0.5 or 1.0 mg. of dimethylstilbestrol. Three rabbits developed papillary cystadenoma of the breast in 10 to 15 months, and in one this progressed to carcinoma within 20 months.

In earlier investigations by Loeb¹¹ it was shown that there is a direct quantitative relationship between the duration of the action of endogenous ovarian hormones and the incidence of carcinoma of the mammary gland in mice; the longer the endogenous hormones were allowed to act, the greater the incidence of carcinoma. It was also shown by Lathrop and Loeb¹² that the latent period preceding the appearance of carcinoma of the mammary gland was in a similar way related to the duration of the action of the endogenous hormones; the longer the endogenous hormones were allowed to act, the shorter the latent period.

It follows from their earlier experiments that removal of the action of

ovarian hormones at a period of life when the mice had passed the onset of sexual maturity was effective in diminishing the incidence of mammary carcinoma and in increasing the latent period.

Shimkin further states: "It is abundantly clear that in all species, carcinoma of the mammary gland is the end-result of an intricate, prolonged interaction and combination of at least several factors or complexes of factors. In all species, a degree of genetic susceptibility and a degree of hormonal stimulation are essential, and the process can be modified by numerous secondary influences of internal and external environment."

What seems to be the double rôle of estrin in the causal and in the formal genesis of mammary cancer resembles what might be the relationship between androgenic substances from the testicle and cancer of the prostate. The beneficial results of removing the ovaries along with a radical operation for cancer of the breast may be attributed to the withdrawal of a causal genesis, to the removal of a formal genesis, or to a combination of both of these factors. The recurrences of cancer of the breast after a radical operation are doubtless due to cancer cells that have been left. The small amount that remains, however, would be stimulated by estrogenic substances. As there have been cases in which cancer of the breast receded, at least temporarily, after removal of the ovaries, with no other treatment, it would seem that there may be a mass relationship. That is, the effect of withdrawing estrogenic stimuli might be greater if there are only a few cancer cells than if there is a large amount. With only a few remaining cancer cells, however, this unfavorable influence of withdrawing the stimulating effect of estrin should be more deleterious and create an unfavorable soil for their existence.

In women who have previously had cancer in one breast, the increase of ovarian activity in pregnancy appears to promote mammary cancer in the remaining breast. Trout¹³ collected 15 instances of pregnancy subsequent to a radical operation for mammary cancer, in 13 of which there was prompt development of very malignant carcinoma in the remaining breast. Wintz¹⁴ reported seven instances of pregnancy after radical operation for mammary cancer, with fatal cancer then occurring in the remaining breast.

Ultimate results from the treatment of cancer of the breast in young women were most disappointing. J. Shelton Horsley found this to be true in his cases prior to 1937. Of nine patients under 36 years of age upon whom a radical operation was performed by him at St. Elizabeth's Hospital in the period from September 1, 1922 to November 1, 1937, five died of recurrence. The marked difference in the results obtained in this younger age-group, as compared with those in older patients, and the results of experimental work already referred to, caused J. Shelton Horsley¹⁵ to adopt the procedure of removing both ovaries whenever a radical operation is done for cancer of the breast in women in the premenopausal period.

Four years after he did the first bilateral oophorectomy associated with radical amputation of the breast, which was on November 19, 1937, the splendid report of Huggins on castration for cancer of the prostate appeared. His

work seems to confirm the wisdom of bilateral oophorectomy in premenopausal women whenever a radical operation is done for cancer of the breast. This procedure apparently was first suggested by Schinzinger,¹⁶ although according to his article, he did not carry it out. He is said to have discussed this also before the Surgical Congress in Berlin on April 25, 1899. Doubtless, it has been performed by other surgeons, although there does not seem to be any systematic record of a number of cases.

At first a bilateral oophorectomy was done with radical operation for cancer of the breast only on patients under 40 years of age. Later, this was extended to all patients in the premenopausal stage. The desirability of having both ovaries removed along with the radical operation is, of course, first explained to the patient.

Since beginning this method of treating cancer of the breast, numerous investigators have reported excellent results by roentgenologic or surgical castration in patients with extensive carcinoma in both the pre- and postmenopausal periods. Ritvo and Peterson¹⁷ reported definite regression of osseous metastases from carcinoma of the breast following ovarian sterilization by roentgenologic treatment. With regression of the metastases there was also marked relief of pain, which was quite similar to the relief of pain in patients with osseous metastases from carcinoma of the prostate.

Treves, *et al.*¹⁸ reported regression of a primary lesion in two cases following bilateral oophorectomy and improvement in another case. They also noted clinical regression in metastases in both the lung and bone, and in several cases there was dramatic relief of pain immediately following castration. Recently, Adair and Herrmann¹⁹ have reported using large amounts of testosterone propionate in treatment of advanced carcinoma of the breast. They reported 11 cases treated, with improvement in four cases associated with relief of pain; no improvement in four cases; and three cases were still under treatment when their report was made. Three of the four cases reported in detail were in their fourth decade, and all of them seemed to show improvement, with a sense of well-being, definite gain in weight, and clinical and roentgenologic evidence of regression of the neoplasms. Two of these three cases were menstruating when the injections of testosterone were started, and after injections developed amenorrhea.

J. Shelton Horsley presented the results up to November 1, 1943, of his cases of radical amputation of the breast with bilateral oophorectomy. A further report on this work is given in the following Tables. In addition to the results obtained on patients in the premenopausal stage, Table I shows results from all cases of cancer of the breast admitted to St. Elizabeth's Hospital between November 1, 1937 and November 1, 1946. These statistics are shown so that the comparison in the different age-groups may be noted.

In Table I there is a total of 170 cases, showing living and no recurrence 108, living with recurrence four, and 54 deaths. Of the dead, 36 were from recurrence, 11 from causes unknown—some of which undoubtedly were from metastases, and seven from causes other than metastases.

CARCINOMA OF BREAST

Table II includes only those cases without oophorectomy, but five of these cases had sterilization by roentgen-ray. There is a total of 131 cases, with no recurrence in 78; living, with local recurrence three. Total deaths were 46, of which 29 were definitely from recurrence; 11 from causes unknown; and six from causes other than metastases.

TABLE I

CANCER OF BREAST

*All cases admitted to St. Elizabeth's Hospital, Richmond, Virginia
between November 1, 1937 and November 1, 1946*

Total cases.....	170
No recurrence.....	108 (63.5%)
Recurrence and living.....	4 (2.4%)
Dead:.....	54 (31.7%)
From recurrence.....	36 (21.2%)
Causes other than metastases...	7 (4.1%)
Cause unknown.....	11 (6.4%)
Follow-up incomplete.....	4 (2.4%)

TABLE II

CANCER OF THE BREAST WITHOUT OOPHORECTOMY

November 1, 1937 to November 1, 1946

All cases without oophorectomy.....	131
No recurrence.....	78 (59.5%)
Recurrence and living.....	3 (2.3%)
Dead:.....	46 (35.1%)
From recurrence.....	29 (22.1%)
Causes other than metastases...	6 (4.6%)
Cause unknown.....	11 (8.4%)
Follow-up incomplete.....	4 (3.1%)

TABLE III

CANCER OF THE BREAST WITHOUT OOPHORECTOMY

November 1, 1937 to November 1, 1946

Cases traced.....	127
No recurrence:.....	78 (61.4%)
Oldest patient—77 years of age	
Youngest patient—28 years of age	
Under 35 years of age—2	
Under 40 years of age—5	
Recurrence and living:.....	3 (2.4%)
Local, after 3 years—1 age 49	
Local, after 2 years—1 age 66	
Local, after 5 years—1 age 35	
Dead:	
From recurrence.....	29 (22.9%) 46 (36.2%)
Causes other than metastases...	6 (4.7%)
Cause unknown.....	11 (8.6%)

Table II is further broken down into Table III, and it will be noted that in patients without recurrence there were several still in the premenopausal stage—two under 35 years of age and five under 40 years of age. Of these five, none had roentgen-ray treatment over the ovaries for one reason or

another, the chief one being a low-grade type of malignancy with either an intraductal or mucoid type in which sterilization seems to be of less value. There are three cases living, with local recurrence, one of whom was in the premenopausal stage at the time of operation and was sterilized by roentgen-ray. However, six months after the first roentgen-ray sterilization, she began menstruating and had to receive roentgen-ray therapy over the ovaries on two other occasions before a complete and final suppression of menstruation was effected. All three recurrence and living cases have had local excision of the recurrent nodules, and recent examinations showed no evidence of further trouble.

Of the 29 deaths from known recurrence, eight cases were in the premenopausal period. One case, age 34, was so extensive that only a diagnostic biopsy was done; three other cases had only the radical operation, and all died within two years. The remaining four cases had roentgen-ray sterilization in addition to the radical operation. Of these four cases, one died after two years, one after four, one after five, and one after nine years. It was because of incomplete castration by roentgen-ray, two of them requiring further roentgen-ray treatment over the ovaries six months later, that it was decided surgical sterilization was the procedure of choice when castration was indicated, with radical amputation of the breast for cancer.

TABLE IV
RESULTS THREE AND FIVE YEARS AFTER OPERATION IN CASES WITHOUT OOPHORECTOMY

	Operated Upon 3, or more, Years	Operated Upon 5, or more, Years
Total cases.....	97	62
Living:.....	55 (56.6%)	28 (45.1%)
No recurrence.....	53 (45.6%)	27 (43.5%)
Local recurrence.....	2 (2.0%)	1 (1.6%)
Dead:.....	42 (43.3%)	34 (54.8%)
From recurrence.....	28 (28.8%)	23 (37.1%)
Causes other than metastases	4 (4.2%)	4 (6.4%)
Cause unknown.....	10 (10.3%)	7 (11.3%)

Realizing that many of these cases have been of recent origin, and a true index of cures is not given in the preceding Tables, the recent cases were eliminated. Table IV gives the results of those without oophorectomy operated upon three years, or more, and five years, or more. There is a total of 62 that have been operated upon five years, or more, of which 28, or 45.1 per cent, are still living. One of these—the patient who had roentgen-ray castration, as mentioned in Table IV—has a local recurrence. There are 34, or 54.8 per cent, dead. Of this number, 23, or 37 per cent, died from recurrence; seven, or 11 per cent, from causes undetermined; and four, or 6 per cent, from causes other than recurrence. Assuming that all of the deaths whose exact cause is not known were from recurrence, there would be a total of 30 deaths, or only 48.4 per cent. Of the patients operated upon three, or more, years ago, which include the cases operated upon five years ago, or more, there is a total of 97; 55, or 56.6 per cent, of whom are still living. Two of these have had

CARCINOMA OF BREAST

local recurrence, but at present there is no evidence of any further metastasis. Of these 97, 42, or 43.3 per cent, have died—28 from recurrence, ten from causes undetermined, and four from causes other than recurrence.

TABLE V

CANCER OF BREAST WITH OOPHORECTOMY

November 1, 1937 to November 1, 1946

All cases with bilateral oophorectomy.....	39	
Living:.....	31 (79.5%)	
No recurrence:.....	30 (76.9%)	
Oldest patient—50 years of age		
Youngest patient—28 years of age		
Average age—40.6 years		
Under 35 years of age—4		
Under 40 years of age—14		
Recurrence:		
Local, after 4.5 years—age 43.....	1 (2.5%)	
Dead:.....	8 (20.5%)	
From recurrence:.....	7 (18.0%)	
After 6 months—1 age 28, bilateral, with metastases to axillae at time of operation		
After 1 year—1 age 38, metastasis to bone		
1 age 38, local metastasis		
1 age 44, extensive axillary involvement at time of operation		
After 2 years—1 age 43, metastasis to lung		
After 3 years—1 age 33, metastasis to bone		
After 5 years—1 age 38, metastasis to lung		
From causes other than recurrence.....	1 (2.5%)	
Age 30, from peritonitis 5 years after operation. Autopsy showed no recurrence		

Table V includes all cases in which bilateral oophorectomy was done at the time of operation, with a total of 39. There have been no recurrences in 30; local recurrence in one; and eight deaths, seven of which were from recurrence and one from causes other than metastasis. The oldest of the living patients was 50 and the youngest 28 at the time of operation. The average age was 40.6 years. There were four under 35 years of age and 14 under 40 years of age. There is one living who has had a local recurrence, the original operation having been done 4.5 years ago, when she was 43 years of age. She has had several recurrences in the skin, occurring at about yearly intervals, the last one being a little over a month ago. The patient at present seems to be in excellent condition, and there is no indication of other metastases. There were eight deaths in the series, seven of which were from definite recurrence and one from general peritonitis following intestinal obstruction five years after the original operation. Necropsy in this case revealed no evidence of recurrence of the malignancy. One case, 28 years old at the time of operation, who had extensive cancer of both breasts, with metastases in both axillae, died six months after operation. The other six cases died of metastasis—three, one year after operation; one, two years after operation; one, three years after operation; and one, five years after operation.

Table VI shows cases three and five years after the original operation, with bilateral oophorectomy. Thirteen cases were operated upon five years ago, or more, and of these, ten are living without recurrence, and one had local skin

recurrence. This gives a percentage of 76.9 living without recurrence after five years. There is a total of 26 that were operated upon three or more years ago, with one local recurrence, as shown in the five-year cases. There were five deaths from recurrence, giving 76.9 per cent of three-year cures, which is the same as that noted in the five-year, or more, cases.

TABLE VI
RESULTS THREE AND FIVE YEARS AFTER OPERATION IN CASES WITH OOPHORECTOMY

	Operated Upon 3 or more Years	Operated Upon 5 or more Years
Total cases.....	26	13
No recurrence.....	20 (76.9%)	10 (76.9%)
Local recurrence.....	1 (3.8%)	1 (7.7%)
Dead from recurrence.....	5 (19.3%)	2 (15.4%)

While this paper is primarily concerned with the results obtained in cancer of the breast cases in the premenopausal stage treated by radical amputation and oophorectomy, we have reviewed in some detail the results obtained in all cases of cancer of the breast admitted to St. Elizabeth's Hospital during this nine-year period. This is done so that the results in those cases without oophorectomy, and mostly in the postmenopausal period, may be compared with those in the premenopausal period, with oophorectomy. This comparison should be significant, as it covers the same period of time, all operations were done by one of three surgeons, and the same operative procedure was used. It will be noted in the five-year "cures" that there were 43.5 per cent in those cases without oophorectomy as compared with 76.9 per cent in those of the premenopausal period with oophorectomy. The same results were observed in the three-year cases in the latter group.

This series of cases, combining bilateral oophorectomy with radical amputation of the breast, is too small to be conclusive, but, in our hands, the results have been outstanding, considering the discouraging reports before oophorectomy was done with the radical amputation. The results are much better than those obtained when roentgen-ray castration was tried, though our few cases treated with roentgen-ray were better than those without either method.

There might be further improvement by the administration of testosterone propionate even after oophorectomy. The recent reports of Adair and Herrmann show that fair results are also obtained by such injections in elderly patients past the menopause with extensive metastases. We have not yet tried these injections either with or without oophorectomy. There have been several reports on the use of testosterone propionate injections without oophorectomy with good results, but as this would be a prolonged procedure it would seem that oophorectomy would be more certain and less hazardous. The objection to the use of the male hormone is quite similar to that of roentgen-ray castration. In some patients sterilization is not complete and the size of the injection or radiation often has to be increased before the desired results are obtained. It is this delay and uncertainty in effecting complete suppression of the female hormone that makes these methods unsatisfactory. Numerous other

factors are involved in the development of breast cancer, such as heredity, the milk factor, *etc.*, as have been shown in experimental and clinical research, but surgical castration of those patients in the premenopausal stage with radical amputation of the breast is a step forward in the right direction.

SUMMARY

1. A brief review of the recent literature on the influence of female hormone on breast cancer has been given.

2. Results obtained by radical amputation of the breast and bilateral oophorectomy in cancer of the breast in premenopausal cases are given, showing 76.9 per cent of cases living without recurrence in both three- and five-year postoperative periods.

REFERENCES

- ¹ Sittenfield, Maurice J.: Sterilization of the Ovaries as an Auxiliary Treatment in Cancer of the Breast. *Radiol. Rev.*, 59, 41, 1937.
- ² Ewing, James: *Neoplastic Diseases*. Ed. 4, Philadelphia, 1941, W. B. Saunders Company, p. 594.
- ³ Lacassagne, A.: Hormonal Pathogenesis of Adenocarcinoma of Breast. *Am. J. Cancer*, 27, 217, 1936.
- ⁴ Huggins, Charles, and Hodges, C. V.: Studies on Prostatic Cancer: I. The Effect of Castration of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. *Cancer Research*, 1, 293, 1941.
- ⁵ Shimkin, Michael B.: Experimental Induction of Mammary Cancer. *Surgery*, 19, 1, 1946.
- ⁶ Loeb, L., Suntzeff, V., Burns, E. L., and Schenken, J. R.: Incidence of Mammary Carcinoma in Mice Treated with Estrogen; Effect of the Age at which the Treatment with Estrogen Begins. *Arch. Path.*, 38, 52, 1944.
- ⁷ Cori, C. F.: Influence of Ovariectomy on Spontaneous Occurrence of Mammary Carcinoma in Mice. *J. Exper. Med.*, 45, 983, 1927.
- ⁸ Murray, W. S.: Ovarian Secretion and Tumor Incidence. *J. Cancer Research*, 12, 18, 1928.
- ⁹ Nelson, W. O.: The Induction of Mammary Carcinoma in the Rat. *Yale J. Biol. & Med.*, 17, 217, 1944.
- ¹⁰ Geschickter, Charles F.: *Diseases of the Breast*. Philadelphia, 1943, J. B. Lippincott Company, p. 274.
- ¹¹ Loeb, L.: *Science*, 42, 912, 1915.
- ¹² Lathrop, A. E. C., and Loeb, L. J.: *Cancer Research*, 1, 1, 1916.
- ¹³ Trout, H. H.: The Remaining Breast after Radical Removal of the Opposite Side for Carcinoma. *Surg., Gynec. & Obst.*, 34, 630, 1922.
- ¹⁴ Wintz, H.: Experiences in the Irradiation of Breast Cancer. *Brit. J. Radiol.*, 31, 150, 1926.
- ¹⁵ Horsley, J. Shelton: Bilateral Oophorectomy with Radical Operation for Cancer of the Breast. *Surgery*, 15, 590, 1944.
- ¹⁶ Schinzinger: Carcinoma of the Mammary Gland. *München. med. Wchnschr.*, 52, 1724, 1905.
- ¹⁷ Ritvo, M., and Peterson, O. S., Jr.: Regression of Bone Metastases after Ovarian Sterilization. *Am. J. Roentgen*, 51, 220, 1944.
- ¹⁸ Treves, N., Abels, J. C., Woodard, H. Q., and Farrow, J. H.: Effects of Orchiectomy on Primary and Metastatic Carcinoma. *Surg., Gynec. and Obst.*, 79, 589, 1944.
- ¹⁹ Adair, Frank E., and Herrmann, Julian B.: The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast. *ANNALS OF SURGERY*, 123, 1023, 1946.

DISCUSSION.—DR. EDWIN P. LEHMAN, Charlottesville, Va.: My remarks are directed only to Doctor Horsley's paper. The general principle underlying the approach to the treatment of possibly curable malignant disease is the destruction of the disease, no matter what anatomic or functional loss is entailed, short of death or degrees of crippling which are worse than the effects of cancer. This principle must be applied in borderline instances with considerable caution. In specific instances it must be finally accepted only when there is proven evidence of effectiveness of the treatment.

In applying this principle to the problem of castration of women with cancer of the breast, we must appraise both the harmful effects of castration and the effectiveness of the procedure. It is, of course, well known that a premature menopause in many women is a serious psychic hazard. In other women, particularly those who have already had children, it may be welcome. I agree with Doctor Horsley that women who have had cancer of the breast should never again become pregnant. Certain women would decidedly prefer castration to the deformity of a radical amputation of the breast, which we do not hesitate to employ without concern about the psychic effects. It is obvious, therefore, that no generalization with regard to the desirability or undesirability of castration will cover all women. If castration is to be employed, it must be used with judgment and particularly with due consideration to the expected psychic result in the individual case. It is undesirable, but so is radical mastectomy. If it has a favorable effect on the cure rate of cancer of the breast in young women, there are certainly many instances in which it can be applied without fear of serious psychic crippling.

The determination of its effect on the prognosis of mammary cancer is not easy. Its application is based, of course, on the well-established endocrine relationships of cancer of the breast in the animal, as outlined by Doctor Horsley. Certain isolated instances of an analogous effect in the human being are on record.

It is natural, of course, that even a single experience of an unmistakably favorable effect will influence the approach of any clinic to this problem. At the University of Virginia Hospital we have under observation a case of eight-year cure without surgical operation. A young woman of 30 with widespread mammary cancer, proven by biopsy from a huge mass in the ipsilateral supraclavicular space, was castrated by roentgen-ray in 1938. This was the only primary treatment. Every visible evidence of tumor disappeared. One year later local roentgen-ray treatment was given. This patient, in 1946, is alive and well, without evidence of disease in the breast itself or in local or distant metastatic areas. Whether or not the local roentgen-ray therapy given in 1939 had an influence on the eight-year cure is not pertinent to the present discussion, since huge masses of tumor disappeared within a short time after castration had been completed. It was this case which led us to carry out castration in certain cases of premenopausal cancer. We have not employed it in all cases but have reserved it for instances in which psychic disturbance was not feared, or in cases presenting inoperable metastases, such as the case cited. During the earlier years castration was done by roentgen-ray. Just as Doctor Horsley has reported, several cases began to menstruate after supposed roentgen-ray castration, and we, therefore, adopted oophorectomy in 1942.

In attempting to appraise results it seems to me that the material must be separated into two groups: namely, castration at the time of radical operation and palliative castration in advanced cases after metastasis has occurred. The former may be called primary castration and the latter secondary. Of the former group we have had 20 cases in which cancer was proven; of the latter, six cases including the case already cited. It is impossible, of course, with only 20 cases over a period of eight years, to measure the results of this procedure on the cure rate. There have been only six cases that were treated more than five years ago and nine cases more than four years ago. In these small subgroups the five-year cures parallel the absence of axillary metastasis.

It is easier to judge the effect of secondary castration, but only if no other therapy is employed. If castration is the only treatment, as in the case mentioned, and marked immediate improvement occurs in a proven tumor, the inference that the treatment is

responsible is fairly direct. In the advanced cases this improvement need not result in a five-year cure to be demonstrative. In our six cases of secondary castration there are only two cases in which castration was not accompanied immediately by other therapy. One of these is the case already reported. In the other there was marked early regression of the lesion without any local roentgen-ray treatment. Death occurred two years later.

Certainly, the experience in our clinic does not yet prove that castration is a justified adjuvant to radical mastectomy. It is our intention to continue to use the method conservatively, however, with the hope that within another five or ten years data will be available to demonstrate the presence or absence of a favorable effect.

Doctor Horsley's interesting paper evidences a similar approach. I wish, however, that he had presented comparisons between cure rates in premenopausal cancer with and without castration, correlated with the extent of disease as the time of treatment, especially as regards axillary involvement. This factor might prove to be more influential upon his excellent rate of five-year cures in a small series than the accompanying castration.

DR. HUGH H. TROUT, Roanoke, Va.: When one has been intensely interested in any subject for 35 years, or more, it is almost impossible not to discuss the subject when it comes up for discussion. However, in order that I may not wander over the face of the earth, I have made some notes so that I might limit my time. It is almost impossible to evaluate the effects of cancer education. In our series of more than 500 there have been 29 women who are the wives of doctors. The time this group allowed to elapse between the time they felt a lump in the breast and the time of reporting the same to their physician averaged nine months; with the women in the rest of the series, this average time was three months. I do not feel that doctors have selected unintelligent women for wives, but I do think the average patient is afraid of cancer and hesitates about reporting the same for fear of what she has heard about the hopelessness of cancer.

One factor has remained very constant over the years; we felt when we were under Doctor Halsted's influence, and later under Doctor Finney's, that the best hope for the cure of cancer was the radical extirpation of the disease *en masse*. That is the "sheet anchor" to which we tied all these years. At present, we are not using preoperative irradiation. Perhaps this is somewhat due to the horrible results of the so-called "Coutard" treatment, with its occasional case of skin necrosis. Frequently, with preoperative irradiation the lump in the breast decreased in size and the patient thought she was improving, and did not report for progress-checks until the growth had again increased in size, and occasionally the malignancy was then farther advanced than when first seen. We do use radiation in young women in rapidly growing malignancy, and particularly if associated with infection. We have felt in a few cases that with preoperative irradiation inoperable cases have been converted into operable cases.

One observation we have made is that if there are one or two large malignant nodes in the axilla, it is a better prognosis than where a chain of small hard shot-like nodes are found. We are still old fashioned enough to flush out the whole field of operation with very hot saline solution. We have the feeling that stray cancer cells, being of very low resistance to heat, might be killed by heat. In addition, the mechanical effects of washing out with large quantities of water might remove some loose cancer cells.

Another observation we have made over the years is that if a node is found under the triangular or falciform fascia which is under the pectoralis minor muscle, the prognosis is bad. Such a finding indicates that the malignancy has extended through the chest wall. Not one of these cases has lived longer than a year, in spite of the fact that no metastasis is shown by roentgenologic studies.

The use of radium at the time of operation we have found of advantage. Just before we close the flaps, we take two long rubber tubes containing radium. We put one of these tubes with radium in the axilla and the other in the region of the distribution of the internal mammary.

We have had something over 170 cases without a single local recurrence. However, this did not improve our five-year "cures" one bit. Eight or ten days after operation we start roentgen-ray treatments, using as many portals of entry as we can. If the skin flaps are not in good condition, such treatment must be postponed. On a recent visit to Boston, I was much interested in talking to the research men working with the one and two million volt machines. My own impression is that we have no reason to expect any improvement, at least at an early date, over the 250,000 volt machine. We do know that these extremely high voltage machines are capable of very wide destruction of both malignant and normal tissue.

In 1931, Peterson, our radiologist, was treating bone metastasis in the pelvis in young women. He was doing this for relief of pain. We were much surprised to see the improvement in the breast condition. The local improvement was truly remarkable. The patient died, but it was interesting that the breast improved by the establishment of the cessation of menstruation. Certainly, irradiation, if properly done, stops the menses and, thus prevents future pregnancy and future lactation. That was the beginning with us of the use of artificial menopause produced by irradiation for the control of malignancy of the breast.

In a recent letter from Frank Adair of New York, he said he had stopped the postoperative use of testosterone propionate except in cases of bone metastasis. We have had no experience with this except in two cases, and neither of these received relief.

I do not know how one can tell definitely what irradiation plus surgery is doing with these cases. I do know our five-year results over this large series of ours, where they have been taken "catch-as-catch-can" have improved since we have been combining irradiation (radium and roentgen-ray) with surgery. We had in a group before 1936, five-year "cures" of 41 per cent; the next five-year group, stopping in 1942, had "cures" of 57.6 per cent. We did not feel that we are seeing earlier cases or that our operative procedures have improved to such an extent as to explain this improvement in these two five-year studies, therefore, we conclude that irradiation has been of benefit in improving our surgical results.

DR. BRADLEY L. COLEY, New York City: We are very fortunate in having three papers dealing with the treatment of cancer of the breast along three accepted lines—surgery; surgery plus irradiation; and hormone therapy. Several aspects of breast cancer are of special interest to the surgeon who is particularly concerned with malignant conditions involving the skeletal system.

I would call attention to the fact that in certain cases the first symptom presented by the patient is referable to bone metastasis; the presence of the primary breast tumor has been wholly unsuspected until after the bone lesion has been demonstrated on roentgenologic examination, and a careful search discloses the primary lesion.

In women who have had radical mastectomy and who later (one to four, or more, years) have complained of backache or pain in a major long bone, the initial roentgenologic examination may be reported as negative. Repeat films are indicated if symptoms persist, and will often subsequently reveal osseous involvement.

The treatment of bone metastasis from breast cancer is wholly palliative. It may consist of (1) roentgen therapy to the affected areas; (2) roentgen or surgical castration; and (3) hormone therapy, using male sex hormone. We still lack sufficient knowledge, based on a large enough series of cases, to state that castration of the premenopausal women is best carried out by oophorectomy or by high voltage roentgen-ray therapy; I suspect surgical castration is more effective.

We know that a substantial proportion of cases of breast cancer, with skeletal metastases, have shown clinical and roentgenographic evidence of improvement following roentgen-ray castration. The clinical improvement has been found to be more striking than that shown roentgenographically, and it may persist for periods ranging from six

to 18 months, or longer. When metastases to nodes or to viscera are considered, the improvement has not been striking.

Testosterone propionate also benefits a substantial proportion of females with breast cancer metastases to bone. On the average, favorable response may persist for about six months, occasionally it lasts as long as 18 months. However, a word of caution is necessary, because a small proportion so treated are made much worse by the administration of male sex hormone owing to the severe hypercalcemia which is induced, so that this method is not without danger.

DR. STUART W. HARRINGTON, Rochester, Minn.: I congratulate the essayists on the splendid presentations that they have given on the results of surgical treatment for carcinoma of the breast. I am pleased that Doctor Finney has emphasized the importance of a thorough radical mastectomy in the treatment of carcinoma of the breast, as I believe this is a very important consideration in the end-results. I wish to compliment Doctor Marshall on the very comprehensive and thorough study he has made as well as on the excellent results he has had in the surgical treatment of carcinoma of the breast.

I have been interested for a number of years in the factors which influence the results of surgical treatment of carcinoma of the breast. Some of the more important factors are as follows: (1) the extent of the malignant involvement at the time of operation; (2) the thoroughness with which the radical operation is done; (3) the degree of malignancy as shown by microscopic examination of the primary lesion; (4) the presence of other associated conditions, such as pregnancy; (5) the general constitutional diseases, such as diabetes; and (6) the age of the patient.

There are unavoidable inaccuracies in statistical studies because of the difficulty in obtaining accurate classifications of cases due to the many factors that influence prognosis. Statistical studies of the results of treatment of mass-groups of patients are often misleading. This is particularly true when comparing the results obtained from different types of treatment; in these studies it is imperative that only similar groups of cases be used for comparison. I do not believe that comparative studies are of value unless it is definitely known that the groups compared are similar as to the type and extent of the disease.

Although axillary nodal metastasis is only one of the factors that may indicate the extent of the disease at the time of operation, I believe it is one of the most important factors indicating the prognosis following operation because of the great influence it has on the survival rates. Because of this fact, in compiling statistical studies of survival rates of malignant disease of the breast, I believe that all cases should be divided into two main groups—those with and those without axillary nodal metastasis at the time of operation.

The importance of the presence or absence of axillary nodal metastasis at the time of operation is shown in a study of 6,149 patients who had radical mastectomy in which 6.5 per cent had axillary nodal metastasis at the time of operation. The patients who did not have axillary nodal metastasis at the time of operation constitute 39.5 per cent of the entire series. The proportion of this group of patients living three years, or more, after operation was 85.0 per cent, or almost twice as large as that for the group with axillary metastasis, which was 45.3 per cent. In the five-, ten-, fifteen-, and twenty-year survival rates of patients without axillary nodal metastasis, it was found that the improvement increased progressively over the group with axillary metastasis. For the five-year period, the survival rate for the group without metastasis was 75.7 per cent, or two and one-half times as large as that for the group with metastasis, which was 30.4 per cent; for the ten-year period it was three and one-half times as large, or 57.9 per cent without metastasis, and 16.4 per cent with metastasis; for the fifteen-year period it was four times as large, or 44.4 per cent without metastasis and 11.1 per cent with metastasis; and for the twenty-year period it was more than five times as large, or 33.5 per cent without metastasis and 6.5 per cent with metastasis.

A quinquennial study was made of unilateral carcinoma of the breast in women who had had radical mastectomy from 1910 to 1938, inclusive. The last period is only four years (1935-1938) because patients operated upon in 1939 had not been operated upon for a sufficient length of time to enable five-year results to be compiled. This study was made up of 5,558 patients, of whom 5,407 were traced. The patients are divided into two groups, those with and those without axillary nodal metastasis at the time of operation. It was found that there was a consistent and appreciable improvement in the results obtained from radical mastectomy in each of the five-year periods. The study of patients presenting axillary nodal metastasis at the time of operation from 1910 to 1914, inclusive, shows that 23.7 per cent were living five years after operation as compared with 39.1 per cent of those upon whom operation was performed during 1935 to 1938, inclusive. In this study the results obtained in patients without nodal metastasis at the time of operation show a greater improvement, in that there was 62.7 per cent of five-year survivals from 1910 to 1914 as compared with 81.9 per cent from 1935 to 1938.

This improvement in the results of surgical treatment was present whether or not the patient had roentgen-ray treatment, and it indicates that the educational program in which the medical profession has participated for many years is becoming effectual in that we are seeing a higher percentage of patients without axillary nodal metastasis.

DR. L. WALLACE FRANK, Louisville, Ky.: In a discussion of cancer of the breast at the meeting of this Association held at Augusta, Georgia, some years ago, I made the statement that I had observed very few cases of skin recurrence. Now I wish to retract that statement, for I have seen quite a number since then. The most remarkable instance of skin recurrence is under my care at the present time. In the Spring of 1926 a radical left mastectomy was performed for cancer of the breast. In the Spring of this year, 1946, she came in to see me on account of a red area in the epigastrium. This was indurated and slightly elevated. The lesion was excised and the specimen was sent to the laboratory. The pathologist made the diagnosis of adenocarcinoma of the breast, recurrent in the skin. So far as I know this is the longest interval between operation for cancer of the breast and skin recurrence.

From January 1st, 1937, to August 1st, 1946, I have performed 136 operations for breast cancer, in my private practice; these were undertaken on 133 patients. One patient developed cancer in the second breast 15 months after her first operation; in a second patient, cancer occurred in the remaining breast four and one-half years after the first operation; in a third instance, the cancer appeared in the remaining breast 18 months after the removal of one breast. This last patient falls into the group of so-called familial cancer. Her maternal grandmother, her mother, and an older sister died of breast cancer; her twin sister died at the age of 21 of the same disease.

Of these 133 patients 56 per cent had proven axillary metastasis at the time when first seen. This figure is comparable to that of Doctor Marshall's series. Such a high incidence of axillary involvement indicates two things: First, that regardless of the dissemination of knowledge of signs and symptoms of cancer among the laity, patients still do not come at an early stage of the disease. Second, and perhaps even more important, is that it demonstrates the fact that the family doctor should be educated to recognize early lesions of the breast. It is only by operating at an early stage of the disease that the curability (and I use this word advisedly) of breast cancer is to be increased.

Between January, 1937, and August, 1944, 105 patients were operated upon. Of the cases with no axillary involvement 80 per cent are alive and well; of those having axillary metastasis 50 per cent show no evidence of the disease.

DR. J. STEWART RODMAN, Philadelphia, Pa.: Adequate skin removal has always been a very important factor in a radical breast amputation. Seventy years ago two very distinguished surgeons in Philadelphia were doing this operation. Samuel W. Gross was

CARCINOMA OF BREAST

doing an amputation by a large circular incision of the breast, and was curing 9.5 per cent of his cases. At the same time, Doctor Agnew, Professor of Surgery at the University of Pennsylvania, said he had removed a carload of breasts and never cured a case. He was removing the breast through a small elliptical incision which sacrificed very little skin. Ever since that time wide removal of skin has been an important feature of this operation. We have found in our own series that only three out of 136, or 2.2 per cent of consecutive cases, showed local recurrence because, we believe, a large area of skin is removed.

It is very important that one should consider the usefulness of the arm, and in the procedure we have done, brought out by W. L. Rodman in 1908, you can get full abduction and extension in all cases. I am not sure that that can be done with any other method as consistently as with this procedure.

A last point is on roentgen-ray treatment. We do not routinely give our patients preliminary roentgen-ray therapy; we do roentgen-ray cases with axillary metastasis, but I am wondering, and would like to ask Doctor Marshall, whether with the use of roentgen-ray he gets an increased number of cases of lymphedema of the arm. We do not know why that happens, but it seems that roentgen-ray may have something to do with it.

DR. WILLARD BARTLETT, St. Louis, Mo.: It was my priceless advantage to have been with Rudolph Virchow in the late nineties, during which time he taught, as you all know, that cancer is a constitutional disease and that the man who once has cancer is bound to die of cancer if something else does not get him along the way. That had just about escaped my recollection until I operated upon a sister of one of my medical friends. She moved to California and I lost track of her. Twenty-six years after the removal of that breast, he wrote me that his sister had died of cancer of the stomach of a cell type different from that found in the breast.

DR. GEORGE G. FINNEY, Baltimore, Md. (closing): I want to thank the discussers of these papers. Dr. Mims Gage just said to me that he is discouraged with the results, and I am frank to say that I agree with him. He has made the suggestion that all women after the age of 40 should have a simple mastectomy as a form of prophylaxis against cancer of the breast. Perhaps this is not such a radical suggestion after all!

DR. HUGH F. HARE, Boston, Mass. (closing): I want to bring out again that our series consisted of 238 consecutive cases of carcinoma of the breast in which large doses of roentgen-ray were administered to each patient. Our series compares favorably with that reported by Doctor Adair, who gave a similar amount of irradiation postoperatively following radical breast dissection. We have given up the idea of doing routine sterilization in the younger age-group because of the psychic effect, but it may be of use in bony metastases in certain instances. If the patient has bone metastases aggravated at the time of the menstrual period and with pain in the opposite breast, then we believe that sterilization by roentgen rays or surgical castration will help. In our experience, it is likely that only between 15 and 25 per cent of the cases will be aided by sterilization. If radiation sterilization is used, an adequate dose should be given to stop all ovarian activity. There is no reason why radiation sterilization should not be as thorough as surgical sterilization.

DR. GUY W. HORSLEY, Richmond, Va. (closing): In reply to Doctor Lehman's question concerning axillary metastasis, of the 39 cases that had surgical castration at the time of the radical operation, 15 had axillary metastasis. Of the ten that are alive and well after five years, four had axillary metastasis at the time of operation, one of these having carcinoma of the breast, bilateral, with metastasis to the axilla.

THE SURGICAL TREATMENT OF SPONTANEOUS CEREBROSPINAL RHINORRHEA*

CLAUDE C. COLEMAN, M.D., AND CHARLES E. TROLAND, M.D.

RICHMOND, VIRGINIA

CEREBROSPINAL RHINORRHEA is the drainage of cerebrospinal fluid through the nose. It is a well-known clinical entity, usually resulting from trauma but which may result from various other causes or even without known cause. The term "spontaneous cerebrospinal rhinorrhea" is very loosely used in the medical literature. The present report is intended to set-up as a distinct group those cases that are truly spontaneous and to report the surgical cure of three such cases.

DEFINITION

Cases of cerebrospinal rhinorrhea have been variously classified by numerous authors, but perhaps the most complete classification is that of Cairns.¹ This author divides the cases into four groups: (1) those resulting from acute head injuries; (2) those occurring as a delayed complication of head injuries; (3) those resulting from nasal operations; and (4) spontaneous cases. He states that most of the cases in his fourth group are due to intracranial tumors but some may be due to congenital anomalies. It is with a subdivision of Cairns' fourth group that this report is concerned. Truly spontaneous or primary cerebrospinal rhinorrhea is the discharge of cerebrospinal fluid through the nose that occurs: (1) in the absence of trauma (acute head injuries, delayed complications of head injuries such as fistulous tracts, operative trauma); (2) in the absence of infection of the bones of the paranasal sinuses (ethmoid caries, sphenoid necrosis, *etc.*); (3) in the absence of tumors eroding the base of the cranium (osteoma, pituitary tumors, meningiomas, *etc.*); (4) in the absence of prolonged increased intracranial pressure (cerebral tumors, congenital or acquired hydrocephalus); and (5) in the absence of demonstrable congenital anomalies (nasal cephalocele, *etc.*). In short, primary cerebrospinal rhinorrhea is the drainage of cerebrospinal fluid through the nose without definite demonstrable cause.

ETIOLOGY

The definition of primary cerebrospinal rhinorrhea given in the preceding paragraph naturally precludes the establishment of a definite etiology for this condition. However, several possible pathways for egress of the fluid from the cranium into the nose have been suggested. Loftus,² and Johnston,³ have suggested that the fluid escapes through the craniopharyngeal canal as rem-

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

nants of this structure can be demonstrated in humans at term. Britt,⁴ and Locke,⁵ have postulated that the olfactory bulb might maintain its embryonic ventricular lumen and a fistula form from this lumen into the nose, probably along the olfactory nerves. Britt⁴ also suggests an opening from the basal subarachnoid cistern through the cribriform plate but does not mention the possible cause of such an opening. Nothnagel,⁶ and Cairns,¹ suggest that fluid may escape along the sheaths of the olfactory nerves. Johnston³ mentions the possibility of holes in the cribriform plate that are deprived of nerve fibers. Adson⁷ and Aubin⁸ suggest congenital defects of the cribriform plate that permit extension of arachnoid along nerve fibers through the cribriform plate.

The most probable pathway for the escape of fluid in the cases of primary cerebrospinal rhinorrhea is along the olfactory nerves. Each olfactory nerve consists of approximately 20 separate filaments which are axons of olfactory cells in the mucous membrane of the nose. These filaments pass through the cribriform plate of the ethmoid *en route* to the olfactory bulb and are held together in bundles by extensions of the three layers of the meninges. The dura mater joins the periosteum of the nose while the pia mater fuses into the neurolemma of the nerves. The arachnoid usually does not extend through the cribriform plate and when it does the extension is very short.

Locke and Naffziger⁹ injected celloidin masses under pressure into the subarachnoid spaces of dogs and noted that there was frequent leakage into the nose. Although this finding could not be duplicated in the human cadaver, it seems probable that in the cases reported here there is an extension of the subarachnoid space along the olfactory nerves into the nose.

It is possible that there is some defective development of the cribriform plate in the cases of primary cerebrospinal rhinorrhea. In the embryo the ethmoidal cartilage consists of a mesial mass which extends from the sphenoid to the tip of the nasal process and of paired masses lateral to the olfactory sacs. The fibers of the olfactory nerve pass between the unjoined mesial and lateral masses. Cartilaginous trabeculae later surround the bundles of nerve fibers and interconnect the three masses. The perforated parts of the completed ethmoid ossify and are then known as the cribriform plates.

The causative agent of the rupture of the arachnoid with consequent escape of fluid, however, is not known. Jauregg¹⁰ has suggested that sneezing might suddenly force open such a pathway. Every theory in the literature for spontaneous rhinorrhea postulates increased intracranial pressure. In the cases reported here there was no evidence of increase in intracranial pressure. The patients did not have respiratory infections or hay fever so that increases in pressure from coughing or sneezing could not play a part. Therefore, although the pathway for the escape of cerebrospinal fluid into the nose is thought to be along the olfactory nerves, the reason for the sudden onset of the rhinorrhea is still unknown.

Although reports of cases of cerebrospinal rhinorrhea abound in the literature, very few of the cases can be properly included in the group here reported. In the reports of Cairns,¹ German,¹¹ Eagleton,¹² and many

others,^{32, 33} there is a definite history of trauma as the etiologic agent of the rhinorrhea. Ten of the eleven cases of Dandy¹³ had histories of trauma or occurred postoperatively. Campbell,¹⁴ Learmonth¹⁵ and Donnelly¹⁶ have reported cases following nasal surgery. Som and Kramer,¹⁷ Adson,⁷ and others, have reported tumors eroding the floor of the skull with subsequent rhinorrhea. Locke,⁵ Meyer,¹⁸ Cushing,¹⁹ and others, have reported rhinorrhea in cases of intracranial neoplasms causing increased intracranial pressure. Aubin⁸ reports minor congenital defects at the cribriform plate. None of these cases fall into the category of truly spontaneous or primary cerebrospinal rhinorrhea set-up in the present report. The great majority of cases reported either have a known etiology or the reports are too meager for proper classification. Of the cases reported by St. Clair Thomson²⁰ only his own case is definitely one of primary rhinorrhea. The remaining cases reviewed had either a definite etiology or insufficient evidence for classification. Johnston³ reported a case and reviewed the literature on rhinorrhea through 1920. Although some of these cases are almost surely primary cerebrospinal rhinorrhea, the case reports, for the most part, are too inadequate for definite classification. The cases of primary cerebrospinal rhinorrhea found in the literature since 1920 are found in Table I. The propriety of including the case of Adson⁷ might well be questioned, as a definite dural defect was found. However, the defect actually was a minor enlargement of the normal opening around an olfactory nerve and as the lesion in the cases here reported is thought to be around the olfactory nerves, it is thought that this case should be included. Two of the cases reviewed showed hyperostosis frontalis interna by roentgenologic examination, but this may have been a coincidental finding. At any rate, the cases are included with reservation.

DIAGNOSIS

Diagnosis of cerebrospinal rhinorrhea is not difficult. Clear fluid drips from the nose almost constantly and if the diagnosis is in doubt, the fluid can be examined by chemical means and shown to be cerebrospinal fluid. Dye can be injected into the lumbar subarachnoid sac and recovered from the nose, as was done by Fox,²¹ and in one of the cases in the present report. This test is also of value in determining the side of the leak, a matter of great importance. After it is established that the fluid is cerebrospinal fluid, it is perhaps best to follow the dictum of Locke² and consider each case as a "brain tumor suspect." Careful history and examination, including roentgenologic studies, will decide whether or not tumor or any increased intracranial pressure plays a part in the etiology. Trauma or operative procedures can be evaluated by the history. Infections of the sinuses and osteomyelitis of the skull can be diagnosed by examination and roentgen studies. Congenital anomalies, likewise, will usually be discovered by adequate study. If all of the above conditions have been discarded by clinical studies, the case must be considered as one of primary cerebrospinal rhinorrhea.

TREATMENT

There is no unanimity of opinion as to the proper treatment of cerebrospinal rhinorrhea. The early writers, such as Loftus² in 1923, felt that any treatment was definitely contraindicated. Feinblatt and Damrau²² in 1934,

TABLE I

Author	Age and Sex	Duration of Rhinorrhea	Side Affected	Mode of Onset	Treatment	Remarks	Results
Adson ⁷ 1941	31 Female	9.5 mos.	Not stated		Craniotomy. Opening 2 mm. in diameter around olfactory nerve. All studies negative.	None	Cure immediately
Friedberg & Galloway ²⁴ 1938	38 Female	4 mos.	Right	Followed severe respiratory infection	Intranasal 20% silver nitrate	All studies negative	Flow ceased in 12 days
Plum ²⁷ 1931	45 Female	18 yrs.	Not stated		Three nasal operations	Had severe headaches. Encephalogram revealed cortical atrophy	Flow has diminished but continues
Fox ²¹ 1933	33 Female	4 mos.	Left	Followed severe respiratory infection	Intranasal 20% silver nitrate	All studies negative	Flow ceased in 4 mos.
Wessels ²⁶ 1939	49 Female	1 yr.	Left	No definite precipitating factor	Craniotomy. Depression in anterior fossa	Evidence of old papilledema; encephalogram was negative	Cure immediately.
Ballou & Ballou ²³ 1937	53 Male	1 yr.	Right	Followed severe respiratory infection	None	Positive WaR. All other studies negative	Flow ceased in 5 mos.
Titche ²⁹ 1941	50 Female	Several mos.	Left	No definite precipitating factor	Told to use silver protein in nose	X-rays revealed hyperostosis frontalis interna	Flow continues
Jobson ²³ 1941	50 Female	2 mos.	Right	Followed sneezing	Intranasal 10% silver nitrate	All studies negative	Flow ceased in 1 day. Recurred 1 year later. Stopped after similar treatment
Dandy ¹³ 1944	39 Male	4 mos.	Not noted	No definite precipitating factors	Craniotomy. Both sides explored	All studies negative	Flow continues
Wurster ³⁰ 1937	29 Female	4 yrs.	Right	Followed severe respiratory infection	Argyrol tampons, mild silver protein solution	All studies negative	Flow ceased in 3 years
Feinblatt & Damrau ²² 1934	59 Female	6 wks.	Not stated	No definite precipitating factor	Rest in bed	All studies negative	Flow ceased in 3 weeks
Ameriso ³¹ 1942	44 Female	15 days	Right	No definite precipitating factor	None	X-rays revealed hyperostosis frontalis interna	Flow continues

felt that any nasal or surgical treatment was contraindicated. However, the extreme danger to life of cerebrospinal rhinorrhea is generally recognized. Certainly, most of the patients with such a leak will eventually develop meningitis, even in spite of modern drug therapy. Rhinologists have tended to treat

cerebrospinal rhinorrhea by intranasal medication and Fox,²¹ Jobson,²³ and Friedberg and Galloway²⁴ have reported cures following the use of silver nitrate, which is painted around the middle turbinate. This method of therapy causes an intense reaction and is open to the objection that intranasal manipulation might well precipitate a meningitis. In addition, intranasal therapy does not attack the rhinorrhea at its most likely source—the cribriform plate. Intracranial operative intervention is the method of choice in the treatment of this condition as modern neurosurgical methods and chemotherapy have largely dispensed with the old objections of danger of meningitis and operative mortality. The exact operative procedure to be followed is still a matter of some debate. Almost all of the surgical methods reported have been directed towards the closing of traumatic fistulae. Cairns¹ employs direct suture of a dural defect or the use of fascia, which has also been advocated by Dandy,¹³ Peet²⁵ and Learmonth¹⁵ have placed iodoform gauze beneath dural defects, while German¹¹ has turned down small dural flaps from the covering of the crista galli. Graham³⁴ plugs the opening in the bone with wax. Adson⁷ uses a bilateral bone flap and sacrifices both olfactory nerves in order to overlap dura around the fistula and interposes muscle in the suture line. All of the above methods, particularly those using an extradural approach, are open to the objection that the dura over the cribriform plate is very thin and adherent.

The method of surgical treatment advocated here postulates that the leakage of fluid is along the olfactory nerves. In none of the three cases was a dural or bony defect seen but the method of treatment outlined as follows produced immediate cures in all cases with no recurrences. A small frontal osteoplastic flap is reflected on the side of the leak, the skin incision being entirely behind the hair line. The dura is opened around the edges of the bony opening and the frontal lobe retracted (Fig. 1). In no case was there any evidence of pressure and it was not necessary to tap the ventricles, ample space for exploration being secured by emptying the basal cisternae. Careful exploration for tumor or congenital defect is then carried out, such exploration being negative in the cases here reported. The filaments of the olfactory nerve are then pulled out of the cribriform plate and a piece of muscle inserted into the openings in the cribriform plate (Fig. 2). The frontal lobe is then allowed to fall back over this area and the dura is tightly closed with interrupted silk sutures. The bone flap is replaced and the skin closed in usual fashion. In all of the three cases here reported the cessation of leakage of cerebrospinal fluid has been immediate and there have been no recurrences. An essentially similar method of attack was used successfully by Sachs in a case reported by Wessels,²⁶ and also by Klein⁸ in two cases with congenital defects at the cribriform plate. The surgical attack and repair should be entirely intradural.

CASE REPORTS

Case 1.—A female, age 40, white, was admitted to Medical College of Virginia Hospital, March 29, 1943, with complaint of fluid running from her nose. Family and past histories noncontributory. Present illness began two months before admission, when

clear fluid began to drip from the left nostril at the rate of five to six drops every half hour. No history of trauma or upper respiratory infection. No headaches, convulsions or evidence of any cerebral involvement. Physical examination on admission was completely negative except for clear fluid dripping from the left nostril. Blood pressure 124/90. Neurologic examination was completely negative. Roentgenologic studies revealed the sella turcica to be normal in size, with the posterior clinoids somewhat thin. There was clouding of the left antrum and right frontal sinus. No roentgenographic evidence of increased intracranial pressure was present. Lumbar puncture revealed an initial pressure of 110 mm. water, with clear fluid. No cells found. Protein normal. Wassermann reaction negative. Blood and urinalysis entirely normal. Sulfadiazine therapy was

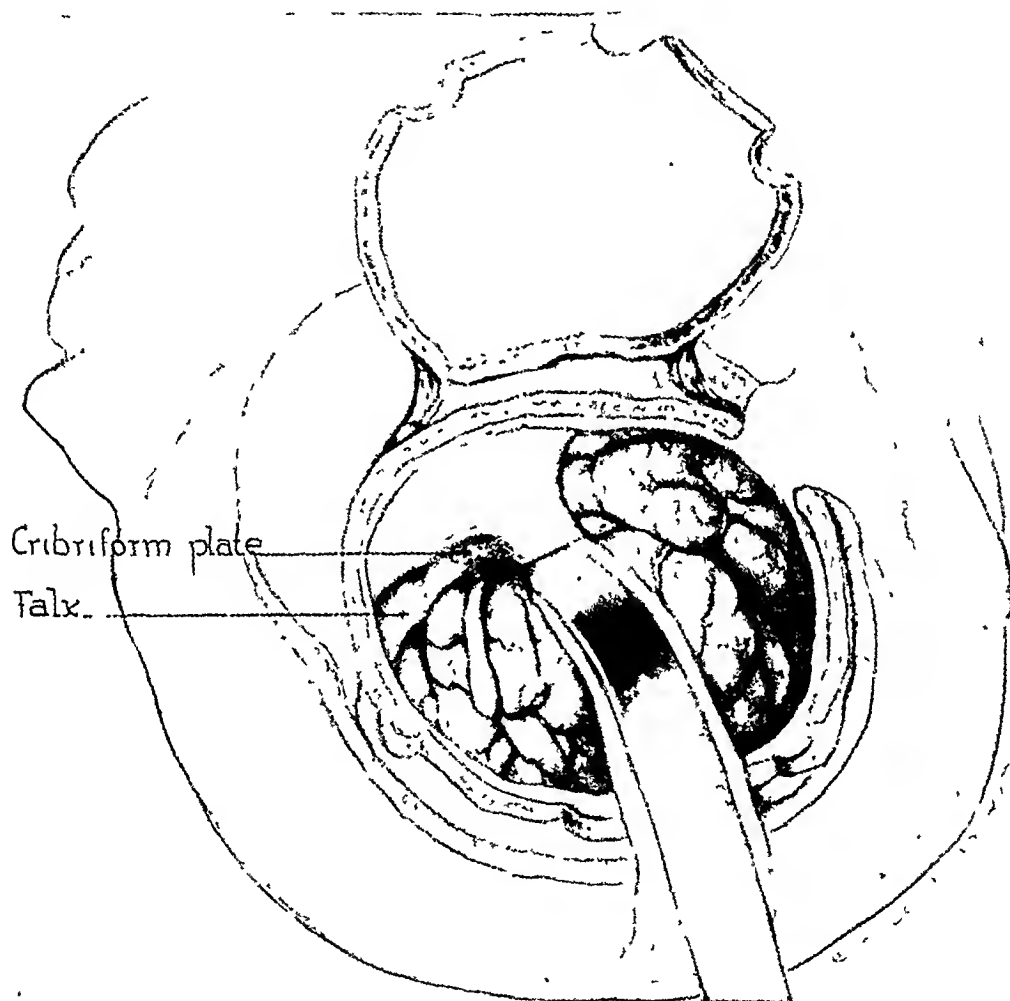


FIG. 1.—Operative exposure of cribriform plate.

instituted. Following lumbar puncture the cerebrospinal fluid ceased to flow. Patient discharged on April 5, 1943. Readmitted April 19, 1943. Eleven days after discharge from the hospital, April 16, fluid again began to drip from left nostril. Patient also complained of severe headache. General and neurologic examinations, again, completely negative. Visual fields full and normal. On April 27 lumbar puncture was done and 1 cc. indigo carmine injected. Fluid from nose was colored blue within 15 minutes. Dry cotton tampons were placed in lateral and superior nasal crevices. Repeated tests showed only the cotton in region of cribriform plate to be discolored. Left frontal craniotomy on April 29, 1943. Technic is outlined in text. No pathology found around sella turcica. The depression of the olfactory bulb seemed a little deep. Cribriform plate sealed-over with

muscle. No drainage of fluid following operation. Patient has continued well in every way (3.5 years postoperative).*

Case 2.—A female, age 50, white, was admitted to Medical College of Virginia Hospital, April 30, 1944, with complaint of watery discharge from left nostril. Family and past histories noncontributory. Present illness began four weeks before admission, with onset of drainage of clear fluid from left nostril. No headache or visual disturbance.

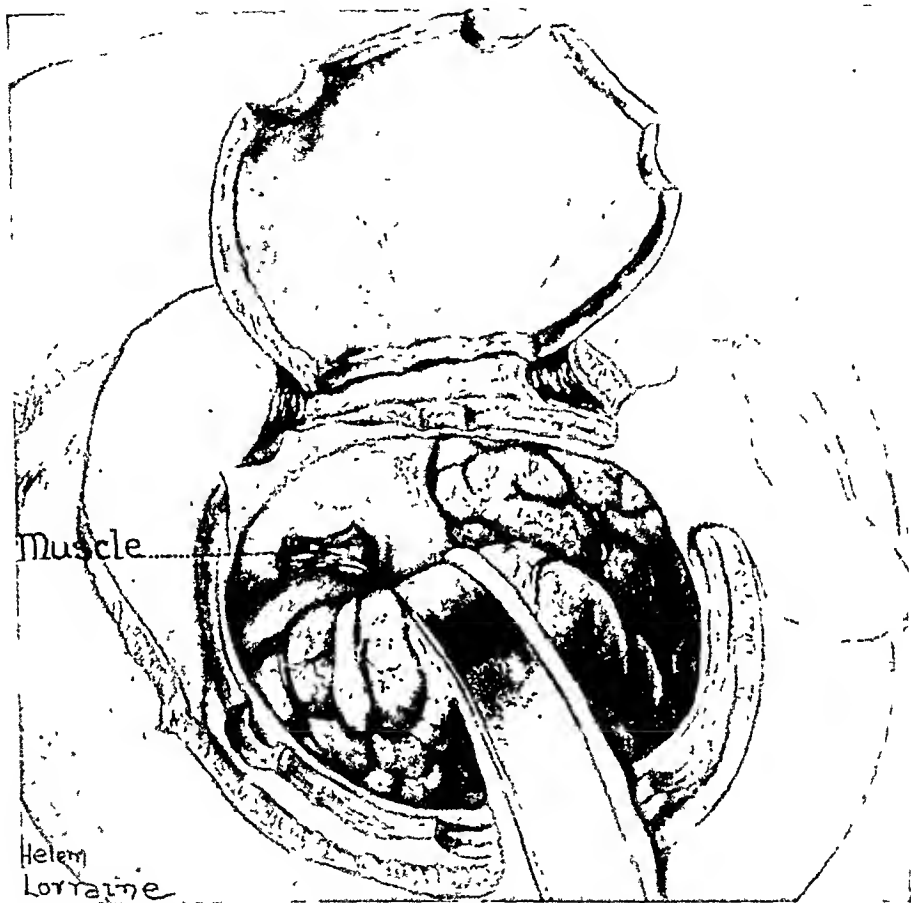


FIG. 2.—Operative exposure illustrating muscle inserted into openings in cribriform plate.

No upper respiratory infection and no history of trauma. Drainage of fluid was constant. General physical examination revealed only drainage of clear fluid from left nostril. Blood pressure 110/80. Neurologic examination was completely negative. Routine blood and urine studies entirely negative. Roentgenologic examination of the skull was entirely negative, the sella turcica being normal in size and not eroded. Ethmoid cells were clear. Rhinologic examination revealed only deflected septum on the left, with deep spur in posterior aspect of middle meatus. Dry cotton localization revealed that fluid was coming from superior nasal space between the middle turbinate and the septum on the left. No anosmia. Operation, May 3, 1944, by technic detailed in text. Operative findings completely negative. Region of left cribriform plate sealed-over with muscle. No further

* See footnote on opposite page.

cerebrospinal rhinorrhea. Discharged May 25, 1944. Patient seen August 22, 1946. Perfectly well (2.25 years postoperative).*

Case 3.—A female, age 50, white, was admitted to Medical College of Virginia Hospital, October 24, 1944, with complaint of drainage of clear fluid from right nostril. Family and past histories were completely negative. Present illness began about two weeks before admission when clear fluid was noted dripping from the right nostril. No upper respiratory infection and no history of trauma. No sneezing. Eleven days after onset of rhinorrhea patient had sudden onset of severe headache and felt that drainage of fluid became more profuse. General physical examination completely negative except for drainage of clear fluid from right nostril. Neurologic examination completely negative. Blood and urine entirely normal by all laboratory studies. Roentgenograms of skull entirely normal. Right craniotomy, October 24, 1944, according to technic detailed in text. No pathology found. Region of cribriform plate sealed-off with muscle. No leakage of fluid following operation. Patient discharged November 10, 1944. October 24, 1946, patient stated that she is perfectly well in every way. (Two years postoperative).

DISCUSSION.—The present report is an attempt to establish as a distinct clinical group those cases of cerebrospinal rhinorrhea that occur without definite demonstrable cause. Although there are innumerable reports of cases of rhinorrhea in the literature, only a few of the cases fall into this category. Undoubtedly, the condition occurs much more frequently than the number of reports indicates, but it seems probable that it is relatively rare. It is desirable to define and segregate these cases as a definite clinical group. The diagnosis, at least for the present, is one of exclusion, as the cases fall into this group only when all demonstrable etiologic agents have been excluded.

A review of the literature reveals 12 cases that fall into the group identified in this report. The great majority of cases have been excluded because of a history of trauma, nasal operations or definite evidence of intracranial tumor. In other instances the cases are too inadequately reported to be sure that they are truly cases of cerebrospinal rhinorrhea or that an intracranial tumor has been eliminated. Five of the cases previously reported had upper respiratory infections either at or immediately before the onset of the rhinorrhea. In none of the cases in this report was there any evidence of such infection. The presence of respiratory infections might well be of some importance because of the suggestion of Werner Jauregg that sneezing might precipitate cerebrospinal rhinorrhea. That such incidents are not the sole precipitating agents is shown, however, by the three cases reported here, in none of which was sneezing a factor.

The etiology of this condition remains in doubt, but it seems most probable that the cerebrospinal fluid escapes along the olfactory nerves. Such a conclusion is given added weight by the cure of the three present cases by intradural occlusion of the points of exit of these nerves with muscle. Very minor congenital anomalies in the region of the cribriform plate can produce openings around the olfactory filaments which allow the arachnoid to extend along the nerves into the nasal cavity. The cause of the rupture of the arachnoid is not

* Cases 1 and 2 were referred by Dr. Roderick MacDonald, of Rock Hill, South Carolina, who reported them in a thesis for the American Laryngological, Rhinological and Otological Society.

as yet determined, however. A marked increase in intracranial pressure could cause the rupture, but in none of the cases in this report was there any evidence of even temporary increased pressure.

Diagnosis of cerebrospinal rhinorrhea is usually not difficult. As mentioned before, it is important to eliminate all possible etiologic agents before the case is considered to be one of primary cerebrospinal rhinorrhea. It is then important to determine the side of the leak, and this can usually be done by inspection of the nasal cavity. Increased certainty is added by the injection of dye into the lumbar canal and viewing its exit into the nose.

Primary cerebrospinal rhinorrhea is an entity that requires prompt treatment. Although some cases have been reported of long duration, they are certainly exceptions to the usual course. The logical point of attack is at the cribriform plate, as this is the almost certain seat of the underlying pathology. The various methods of surgical approach have been reviewed in the text and the authors' method detailed. By this method the presumed seat of pathology is directly attacked and only one olfactory nerve is sacrificed. The efficacy of this method of attack is attested by the results obtained in three cases.

SUMMARY

1. A group of cases exhibiting cerebrospinal rhinorrhea without demonstrable cause is defined as primary cerebrospinal rhinorrhea and set-up as a clinical entity.
2. The literature is reviewed and 12 cases tabulated as probably belonging to this group.
3. Possible sites for escape of cerebrospinal fluid into the nose are discussed and the probable site suggested.
4. A surgical treatment for this condition is detailed, and three cured cases reported.

BIBLIOGRAPHY

- ¹ Cairns, H.: Injuries of the Frontal and Ethmoidal Sinuses: With Special Reference to Cerebrospinal Rhinorrhea and Aeroceles. *J. Laryng.*, 52, 589-623, 1937.
- ² Loftus, J. E.: Cerebrospinal Rhinorrhea: Report of a Case. *J. A. M. A.*, 80, 841-842, 1923.
- ³ Johnston, W. H.: Cerebrospinal Rhinorrhea: The Study of One Case and Reports of Twenty Others Collected from the Literature Published Since 1900. *Ann. Otol. Rhinol. and Laryng.*, 35, 1205-1240, 1926.
- ⁴ Britt, R. E.: Rhinorrhea and Neoplasms of the Central Nervous System. *J. Nerv. and Mental Dis.*, 81, 654-661, 1935.
- ⁵ Locke, C. E.: The Spontaneous Escape of Cerebrospinal Fluid through the Nose. *Arch. Neurol. and Psych.*, 15, 309-324, 1926.
- ⁶ Nothnagel, H.: Geschwulst der Vierhügel; Hydrocephalus; Abfließen von Cerebralfüssigkeit durch die Nase. *Wien. med. Bl.*, 11, 161, 193, 225, 1888.
- ⁷ Adson, A. W.: Cerebrospinal Rhinorrhea: Surgical Repair of Craniosinus Fistula. *ANNALS OF SURGERY*, 114, 697-705, 1941.
- ⁸ Aubin, A., Martin, R., Klein, H., and Sureau: Un cas de rhinorrhée cerebrospinale; guérison par intervention chirurgicale. *Ann. d'oto-laryng.*, 6, 147-150, 1944.

- ⁹ Locke, C. E., and Naffziger, H. C.: Cerebral Subarachnoid System. *Arch. Neurol. and Psychiat.*, 12, 411-415, 1924.
- ¹⁰ Juaregg, W.: Vom Niese. *Wien. Med. Wochnsch.*, 86, 9-12, 1936.
- ¹¹ German, W. J.: Cerebrospinal Rhinorrhea: Surgical Repair. *J. Neurosurg.*, 1, 60-66, 1944.
- ¹² Eagleton, W. P.: The Cerebrospinal Fluid as an Aid to Diagnosis and Treatment of Inflammatory Diseases. *J. Laryng. and Otol.*, 44, 721-725, 1929.
- ¹³ Dandy, W. E.: Treatment of Rhinorrhea and Otorrhea. *Arch. Surg.*, 49, 75-85, 1944.
- ¹⁴ Campbell, E. H.: Cerebrospinal Rhinorrhea following Intranasal Surgery. *Ann. Otol., Rhinol., and Laryngol.*, 37, 865-872, 1928.
- ¹⁵ Learmonth, J. R.: Cerebrospinal Rhinorrhea Treated by Operation. *Proc. Staff Meetings Mayo Clinic*, 4, 115-116, 1929.
- ¹⁶ Donnelly, J. C.: Cerebrospinal Rhinorrhea. *Arch. Otolaryng.*, 16, 350-359, 1932.
- ¹⁷ Som, M. L., and Kramer, R.: Cerebrospinal Rhinorrhea. *Laryngoscope*, 50, 1167-1174, 1940.
- ¹⁸ Meyer, A.: Escape of Cerebrospinal Fluid through the Nose. *J. Nerv. and Ment. Dis.*, 31, 216-221, 1903.
- ¹⁹ Cushing, H.: Acoustic Neuromas. *Laryngoscope*, 31, 209-240, 1921.
- ²⁰ Thomson, St.C.: The Cerebrospinal Fluid: Its Spontaneous Escape from the Nose. Cassell and Co. London. 1899.
- ²¹ Fox, N.: Cure in a Case of Cerebrospinal Rhinorrhea. *Arch. Otolaryng.*, 17, 85-86, 1933.
- ²² Feinblatt, H. M., and Damrau, F.: Cerebrospinal Rhinorrhea. *Med. Rec.*, 139, 324-326, 1934.
- ²³ Jobson, G. B.: Spontaneous Cerebrospinal Rhinorrhea. *Penn. Med. J.*, 44, 1275-1276, 1941.
- ²⁴ Friedberg, S. A., and Galloway, T. C.: Spontaneous Cerebrospinal Rhinorrhea. *Ann. Otol., Rhinol. and Laryngol.*, 47, 792-794, 1938.
- ²⁵ Peet, M. M.: Symptoms, Diagnosis, and Treatment of Acute Cranial and Intracranial Injuries. *N. Y. State J. Med.*, 28, 555-562, 1928.
- ²⁶ Wessels, A.: Report of a Case of Spontaneous Cerebrospinal Rhinorrhea with Operative Cure. *Ann. Otol., Rhinol. and Laryngol.*, 48, 528-530, 1939.
- ²⁷ Plum, F. A.: Cerebrospinal Rhinorrhea: Report of a Case with a History of 18 Years' Duration. *Arch. Otolaryngol.*, 13, 84-86, 1931.
- ²⁸ Ballou, D. H., and Ballou, H. C.: Cerebrospinal Rhinorrhea. *Arch. Otolaryngol.*, 25, 57-62, 1937.
- ²⁹ Titcher, L. L.: Cerebrospinal Rhinorrhea: Report of a Case Presenting Hyperostosis Frontalis Interna. *Ann. Otol., Rhinol. and Laryngol.*, 50, 554-560, 1941.
- ³⁰ Wurster, H. C.: Cerebrospinal Rhinorrhea. *J. Indiana State Med. Assn.*, 30, 199-201, 1937.
- ³¹ Ameriso, A. M.: Craneorrinorrea por hiperostosis frontal interna. *Rev. otorrinolaring. d. litoral.*, 1, 319-324, 1942.
- ³² Coleman, C. C.: Fracture of the Skull Involving the Paranasal Sinuses and Mastoids. *J. A. M. A.*, 109, 1613-1621, 1937.
- ³³ Gurdjian, E. S., and Webster, J. E.: Surgical Management of Compound Depressed Fracture of Frontal Sinus, Cerebrospinal Rhinorrhea and Pneumocephalus. *Arch. Otolaryng.*, 39, 287-306, 1944.
- ³⁴ Graham, T. O.: Clinical Records. *J. Laryngol. and Otol.*, 32, 344-347, 1937.

DISCUSSION.—DR. FRANC D. INGRAHAM, Boston, Mass.: It is a great pleasure to hear this interesting paper by Doctor Coleman and Doctor Troland on rhinorrhea which seems to be spontaneous. Since it is a relatively uncommon condition I might add a word about three similar patients seen on our service. All three were female patients and in two instances the onset was associated with sneezing during the course of a respiratory infection. One patient had severe hypertension and exploration was considered unwise. The leak stopped spontaneously and somewhat later she succumbed to cardiovascular disease. At autopsy, a very careful examination of the cribriform plate was made but no abnormal opening was demonstrated. In the second case a congenital defect, perhaps 5 mm. in diameter, was exposed at operation although it could not be seen in the roentgenograms. In the third case a fracture was demonstrated although there had been no history of trauma elicited. It would seem likely that injury might be a causative factor in some of these cases although nothing in the history would point to it. As far as treatment is concerned, Doctor Coleman and Doctor Troland have shown that this technic is effective and has the great advantage of preserving the olfactory endings on one side.

DR. BARNES WOODHALL, Durham, N. C.: I am sorry Doctor Coleman could not be here and I trust that he will soon recover from his distressing accident. I am delighted to discuss this paper, since Doctor Troland is an old friend and colleague of mine.

However, I know little about this rare neurosurgical problem. After reading the title of this paper on the program, I reviewed our material and could find only two cases that could be defined as possibly primary cerebrospinal rhinorrhea. On further study, the first case was proven to be a stenosis of the aqueduct of Sylvius and the rhinorrhea ceased following a Trokildsen's procedure performed by Dr. Guy Odom. The second case was that of a woman, age 50, who sneezed vigorously and immediately developed a profuse rhinorrhea. At that time I investigated the pertinent literature and found that, among the few things that could be done, was the application of silver nitrate in the nose. However, she was placed in a sitting position following several spinal punctures and the rhinorrhea ceased and she has not returned to our hospital. I am very glad to know about Doctor Troland's findings in this perplexing syndrome and I shall be guided by them in the future if I should encounter another case.

DR. ERNEST SACHS, St. Louis, Mo.: We have had two cases which may truly be classed as spontaneous cerebrospinal rhinorrhea. One was operated upon by Doctor Furlow and one by myself. I think, in the first place, he is absolutely right. This condition must be attacked intracranially and attacked promptly. In the second place, until we get further information, it would seem the best thing to do, which is what we did in our cases, is to remove the olfactory fibers on the side on which the leak occurs and plug the bone with some substance, such as muscle. We think muscle is better than fibrin foam or fascia. We found no evidence of congenital defect and no etiologic factor in our cases; both patients were women. Just why that should be I do not know. Certainly, it is all important to tackle the thing from the intracranial approach and do it promptly and not let them continue to leak, even though an occasional one might heal spontaneously.

DR. CHARLES E. TROLAND, Richmond, Va. (closing): I want to express my appreciation to Doctors Ingraham, Woodhall and Sachs for their discussion. In one of the cases we reported the patient stopped leaking fluid following lumbar puncture but soon came into the hospital again leaking fluid. Personally, I believe it is increased intracranial pressure that causes rupture of the arachnoid, but in no case could we definitely determine what caused the increased pressure. We agree with Doctor Sachs that muscle rather than fascia is the proper tissue to be used, and definitely feel that fibrin foam and gelatin foam are not as desirable materials as muscle.

TETRA-ETHYL-AMMONIUM AS AN ADJUNCT IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE AND OTHER PAINFUL STATES*

FREDERICK A. COLLIER, M.D., KENNETH N. CAMPBELL, M.D.,
ROBERT E. L. BERRY, M.D., MARTIN R. SUTLER, M.D.,
RICHARD H. LYONS, M.D., AND GORDON K. MOE, M.D.

ANN ARBOR, MICHIGAN

FROM THE DEPARTMENTS OF SURGERY, MEDICINE, AND PHARMACOLOGY,
UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN

THE DEMONSTRATION by Acheson and Moe^{1, 2} that in animals the tetra-ethyl-ammonium ion† will block transmission of nerve impulses through autonomic ganglia led to extensive investigations of the effects of this drug in man. Preliminary observations of its usefulness as a diagnostic and therapeutic agent in various disease states have been previously reported by Lyons,^{3, 4} Berry, and coworkers.⁵

It is the purpose of this report to present in detail the clinical observations derived from a large series of patients suffering from peripheral vascular disease and allied disorders who received one or more injections of tetra-ethyl-ammonium for the purpose of producing an autonomic blockade, and to attempt to clarify from the results obtained the exact rôle played by the autonomic nervous system in these particular disease states and the benefits to be derived from single or multiple autonomic blockades.

PHARMACOLOGY OF TETRA-ETHYL-AMMONIUM

Sufficiency data¹⁻⁴ has been made available to make unwarranted any detailed description of the pharmacology of the tetra-ethyl-ammonium ion in this paper. Suffice to say that the ganglionic blocking action of tetra-ethyl-ammonium has been shown to be its most prominent effect when administered parenterally to animals. A brief consideration of the clinical and pharmacologic observations supporting this contention may be listed as follows:

1. Following the parenteral injection of tetra-ethyl-ammonium there is a fall in both systolic and diastolic blood pressure. This is not the result of the direct action of the drug upon the arterioles since intra-arterial injection produces no change, whereas intravenous injection produces an increase in peripheral blood flow. This increase in peripheral blood flow may be demon-

* Presented, in part, before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

Supported, in part, by grants from Life Insurance Medical Research Fund and by Parke, Davis & Co.

† Furnished as tetra-ethyl-ammonium chloride ("Etamon") by Parke, Davis and Company, Detroit, Michigan, in 20-cc. sterile ampules, through the courtesy of Dr. E. C. Vonderheide.

strated clinically either by plethysmographic recordings or controlled thermocouple studies.

2. The drug produces no further fall in blood pressure after destruction of the medulla or transection of the cervical cord in the experimental animal (vasomotor tone absent). If the transected cervical cord, however, is stimulated, thus, restoring vasomotor tone, the injection of tetra-ethyl-ammonium will then produce a fall in blood pressure.

3. The injection of tetra-ethyl-ammonium does not prevent the direct peripheral action of epinephrine even where the latter is infused to produce a restoration of blood pressure after destruction of the vasomotor center of the medulla. Despite the restoration of blood pressure by the administration of epinephrine, the depressor response to tetra-ethyl-ammonium is still held in abeyance.

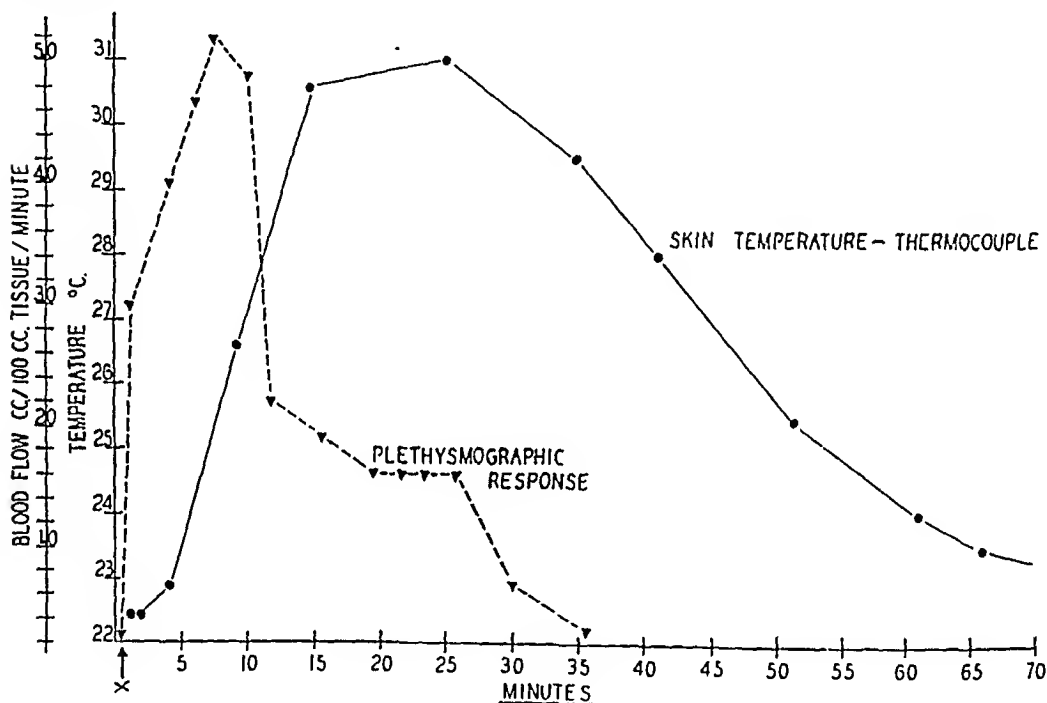


FIG. 1.—Peripheral blood flow response (foot) in a patient with functional vascular disease as measured by plethysmography and skin temperature (thermocouple) recordings following the intravenous administration of 500 mg. tetra-ethyl-ammonium. Note the delay in thermal response and the marked increase in blood flow from 0.24cc./per minute/per 100 grams of tissue to 5.2 cc./per minute/per 100 grams of tissue.

4. In animals, following the administration of the drug, preganglionic stimulation (stellate) produces no change in heart rate. Postganglionic stimulation under identical conditions produces a slowing of heart rate, evidence that the site of action of the drug lies within the ganglion.

5. Following parenteral administration of tetra-ethyl-ammonium, preganglionic stimulation of the cervical sympathetics to the nictitating membrane in animals is ineffective in producing a contraction of this membrane. Under identical conditions, however, postganglionic stimulation is effective, further evidence that the site of action of the drug lies within the ganglion.

6. Peripheral blood flow to the extremities as measured by plethysmography or thermocouple temperature recordings is increased following the injection of the drug in man (Fig. 1).

7. In man, in addition, there is dilatation of the pupil, loss of accommodation, cessation of sweating, dry mouth, and postural hypotension for varying periods of time following the injection of the drug.

8. Tetra-ethyl-ammonium produces cessation of gastro-intestinal motility as observed fluoroscopically and by roentgenograms,²⁰ and atony of the bladder as measured by cystometric studies.⁶

9. The pain of angina pectoris and coronary thrombosis is obliterated following injection of tetra-ethyl-ammonium in spite of a possible decrease in coronary blood flow and a definite further fall in blood pressure. Other types of visceral pain are likewise ameliorated.⁴

10. Clinically, no action of the drug can be demonstrated in a sympathectomized extremity, whereas evidence of sympathetic block can be demonstrated in a normal control extremity in the same individual.⁵

CLARIFICATION OF TERMINOLOGY

The term "vasospasm" is used herein to refer to an *abnormal* degree of vasoconstriction of blood vessels which is manifested by the clinically-evident signs and symptoms of coldness, hyperhidrosis, mild cyanosis and pain.

The term "functional component" is used herein with reference to the presence or absence of vasodilation or vasoconstriction, which are expressions of normal physiologic function. If a blood vessel is capable of vasodilatation a functional component is said to be present. In the presence of marked organic changes in the blood-vessel wall, *i.e.*, arteriosclerosis or thromboangiitis obliterans, the vessel may be incapable of undergoing dilatation, hence, the functional component is said to be absent.

The term "autonomic blockade" is used with reference to the temporary paralysis of the ganglia of the autonomic nervous system following the injection of tetra-ethyl-ammonium.

METHOD OF STUDY EMPLOYED

Details of the clinical use of tetra-ethyl-ammonium for diagnostic and therapeutic autonomic blockade have been reported elsewhere.^{4, 5} In brief, the patient is placed in a recumbent position, extremities uncovered, in a room of suitable and preferably constant temperature (68°-75°F.). Thermocouple temperature recordings for control were taken from symmetrical points of the extremities under study. Measurements from the peripheral portion of the digits have been usually taken for graphic recording (Fig. 2). Following suitable control studies, tetra-ethyl-ammonium (chloride or bromide) was injected intravenously or intramuscularly in a 10 per cent solution. The intravenous dose employed ranged from 100 mg. (1 cc.) to a maximum of 500 mg. (5 cc.). Considerable care was taken as regards the rate of injection, a minimum of 15 to 60 seconds being ordinarily employed and constant observation of the pulse volume and general reaction of the patient being utilized as a guide to cease or delay further administration of the drug. *Under no circumstance was more than 500 mg. (5cc.) employed as the intravenous dose.* It should be pointed out that this amount of the drug is not always necessary to produce an autonomic blockade, in elderly patients with advanced arteriosclerosis or

in labile patients with functional vascular disease, both of whom are sensitive to autonomic blockade. Previous experience with the reaction of the patient to the injection of the drug was found to be the safest guide in subsequent administrations. It was noted that many patients experienced little difficulty from the injection of tetra-ethyl-ammonium if they had had previous experience with autonomic blockade carried out in this fashion, tolerating maximal doses (5cc.) without untoward systemic effects.

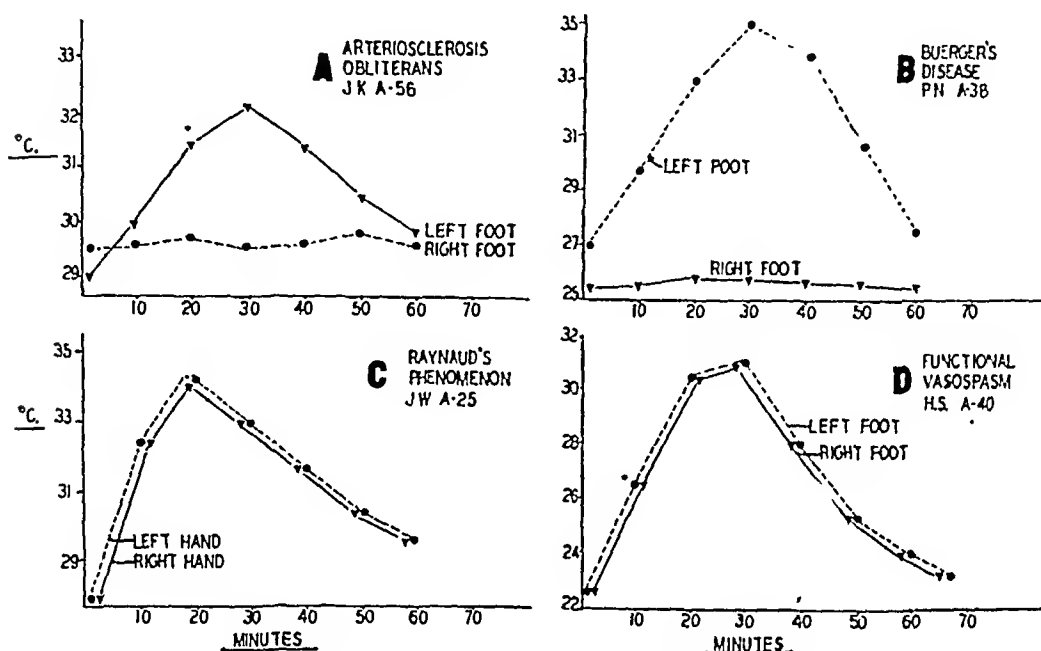


FIG. 2.—Peripheral skin temperature responses in patients with organic and functional vascular disease measured at a room temperature between 68°–70°F. before and after ganglionic block with tetra-ethyl-ammonium.

A. Arteriosclerosis obliterans. The response in the right foot demonstrates marked occlusive changes with an absence of vasodilatation. The left foot has a normal response.

B. Buerger's disease. The right foot is the site of advanced occlusive changes. A marked functional response is present in the left foot.

C. Raynaud's phenomena. The right and left hands demonstrate an equal temperature response. No evidence of organic occlusion.

D. Functional vasospasm. Starting with an initially low temperature, the right and left foot respond equally without evidence of organic occlusion.

At times it has been noted that the initial injection of tetra-ethyl-ammonium does not produce satisfactory effects in patients in whom it would be reasonable to assume that such a blockade should be effected. Often, however, a satisfactory response can be obtained by repeating the injection on subsequent days. The explanation of this phenomenon is not clear. The rapid excretion of tetra-ethyl-ammonium makes untenable the postulation that this is a cumulative effect of the drug. The presence of fear on the part of the patient with an increased out-put of adrenalin might conceivably nullify the action of tetra-ethyl-ammonium.

THE DIAGNOSIS OF CAUSALGIA AND SYNONYMS APPLIED TO RELATED STATES

Little if anything has been added to the original description of causalgia written by Mitchell in 1864. The frequent finding of osteoporosis in the affected extremity (Sudek's atrophy) and the definite rôle of the sympathetic nervous system as regards the propagation of pain (Leriche) have been little added to over the ensuing year. However, as a result of various authors describing different stages of the same process, a variety of synonyms has accumulated, each of which, in a sense, represents a type of what is more widely recognized as being causalgia, but, in essence, not necessarily having the exact features originally described by Mitchell. To cite a few,^{7, 8, 10, 11} acute atrophy of bone, stupeur arterielle, reflex arterial spasm, trophic edema of bone, minor causalgia, traumatic vasospastic dystrophy, reflex sympathetic dystrophy, chronic traumatic edema, peripheral trophoneurosis, posttraumatic osteoporosis, and Sudek's atrophy have all been used to designate either the original state, as described by Mitchell, or a manifestation of the same process. It is recognized, for example, that early in the course of events, vasodilatation may be present and bone atrophy absent. Later, vasoconstriction (vasospasm) and osteoporosis are more frequently encountered.

From the history or examination of the patient, the following sequence of events will usually establish a diagnosis of causalgia or reflex sympathetic dystrophy.^{7, 8, 15} These findings and history represented the basis for diagnosis in this series:

1. A history of previous trauma, sometimes almost insignificant and usually, but not necessarily, involving periarticular, vascular or nerve tissues (venous thrombosis, lacerations, gunshot wounds, old fractures, sprains, dislocations, phlebitis or periphlebitis, hematomas, crushing injuries, burn scars, puncture wounds, amputations, etc.).

2. Abnormal or disproportionate prolongation of pain, usually directed peripherally to hand or foot, following no known anatomic distribution of nerves, and typically of a burning or aching character which may progress in severity and is characteristically aggravated by manipulation, temperature change, auditory, visual and emotional stimuli.

3. The occurrence of vasomotor phenomena over a time-interval disproportionate to the initial trauma with a tendency toward diffusion and extension. Early vasodilatation, temperature change, color change, hyperhidrosis, edema. Later, evidence of vasoconstriction (vasospasm), chronic periarticular edema and fibrosis, atrophy, hyperhidrosis, osteoporosis and waxy pallor, with almost pathognomonic hygromania in the severe cases.

4. A frequent affectation of the morale of the sufferer (Leriche).¹¹ (Anxiety states, psychoneuroses, suicidal tendencies, drug addiction, inferiority patterns).

5. The frequent roentgenographic demonstration of early cystic or late diffuse osteoporosis in the involved extremity, (Sudek's atrophy) usually in association with immobilization, atrophy, periarticular fibrosis and ankylosis of joints. This must be differentiated from osteoporosis due to other causes.

6. Cessation of pain and/or amelioration of the clinical picture following blocking or extirpation of the sympathetic ganglia supplying the involved

areas. (Leriche,¹¹ de Takats,⁷ Mahorner,⁹ Allbritten,¹² Evans,⁸ White,¹⁰ *etc.*). Certain advanced cases may have no relief (subjectively) of their difficulties despite sympathectomy, rhizotomy or even cordotomy. Under such circumstances, the pain is said to be "thalamic" and will respond, if at all, only to sensory decortication.⁷

Table I summarizes the results of treatment with tetra-ethyl-ammonium of six patients classified as having a true causalgia.

Patients with causalgia and related states may not present themselves for examination with all of the diagnostic features listed. Pain may actually be absent or minimal despite all of the other signs of causalgia being present. Such a situation has given rise to the term "reflex sympathetic dystrophy."⁸ The occurrence of edema may be the outstanding feature—hence, the synonym chronic posttraumatic edema. In general, however, if the time elapsed has been sufficient, other collateral evidence is usually available and no difficulty is encountered in correctly classifying the patient's malady. Table II summarizes the results of treatment of 14 patients with tetra-ethyl-ammonium classified under the category of posttraumatic painful states.

The following case reports are presented to illustrate the utilization of tetra-ethyl-ammonium as a diagnostic, prognostic and therapeutic measure in patients with causalgia and posttraumatic painful states.

CASE REPORTS

B. S., Col. male, age 53. Patient was admitted to the Neurosurgical Service, 8-29-'46, complaining of severe pain in the left hand and forearm. He gave a history of receiving a shotgun injury to the left upper arm, 1-11-'46, which was operated upon elsewhere. The details of this procedure were not known. The patient experienced pain immediately following the operation which had gradually increased in intensity to the point where he was unable to move the left upper extremity for fear of aggravating the pain. He experienced some relief by constantly keeping the hand covered in a moist towel (hygro-mania). The pain was of a burning, aching character and unlocalized.

Examination revealed a colored male carefully guarding his left upper extremity, the hand of which was wrapped in a wet towel. He had the typical facies of a patient in constant pain. Detailed examination of the hand and arm was impossible. There was a healed scar on the posteromedial aspect of the left upper arm. The skin was smooth and shiny and obvious atrophy of musculature was present. There was incomplete ankylosis of the elbow, wrist and joints of the hand. The skin of the hand was hyperesthetic to stimulation, and the elbow and hand were maintained in a flexed position. A marked temperature gradient was present, as was evidence of excessive sweating (seen later). Later examination revealed complete ulnar and incomplete median nerve palsy. Roentgenologic examination revealed marked patchy osteoporosis involving the distal ends of the radius and ulna, the bones of the wrist and hand being extensively involved with the exception of the proximal portion of metacarpals 2-5, inclusive. This was interpreted as being a Sudek's type osteoporosis.

The patient received tetra-ethyl-ammonium, I. V., 250-500 mg. on four occasions for the purpose of producing a sympathetic block. Following each of these administrations, pain ceased for a varying interval of time and the patient was able to carry out joint movements with greater ease. Accordingly, 9-7-'46, an upper dorsal sympathectomy was performed. Immediate relief of pain was experienced by the patient. Exploration of the median and ulnar nerves in the scar site was contemplated for the near future.

TABLE I
SUMMARY OF THE RESPONSE TO TREATMENT WITH TETRA-ETHYL-AMMONIUM IN PATIENTS WITH CAUSALGIA

Case Name	Age	Sex	Etiologic or Initiating Factors	Duration Pain or Symptoms	Auto-nomic Blocks* grams	Number Total	Duration Treatment	Result of Treatment and Duration of Benefit	Final Diagnosis	
3	B.D.	19	F	Gunshot wound of thigh, peroneal palsy (partial).	12 mos.	11	5,500	Periodic +. 1 week daily I.V.	Immediate cessation pain, which lasted few hours. Gradual increase in duration relief. Discharged ambulatory and free of pain.	Causalgia (lower extremity) following gunshot wound of thigh with partial peroneal nerve palsy.
5	E.D.	48	F	Crush injury of finger.	25 mos.	17	8,500	3 weeks Daily I.V.	Definite relief of pain and amelioration of edema, with improvement in joint motion and use of extremity (temporary).	Causalgia (upper extremity) following crush injury of finger. Psychoneurosis. Sympathectomy indicated but not advised. (See case history.)
7	L.L.	34	F	Minor burn of finger, subsequent cellulitis hand. Abscess forearm, chronic drainage.	7 mos.	6	3,000	1 week Daily I.V.	Patient admitted temporary alleviation pain following each injection but required frequent administration opiates.	Causalgia following chronic tenosynovitis forearm. ?Median palsy. Morphine addiction. (See case history.)
8	M.L.	59	F	Old fracture. Dislocation head of radius.	2 mos.	6	8,700	1 week Daily I.V. and I.M.	Definite temporary improvement (5 hours/injection) in symptoms. Later gradual disappearance original pain.	Causalgia (upper extremity) following old fracture—dislocation, with partial median nerve palsy. Resection radial head advised.
18	B.S.	53	M	Gunshot wound left arm. Radial-ulnar palsy.	8 mos.	4	1,600	1 week I.V.	Temporary cessation pain (3-5 hours/injection). Sympathectomy, with relief pain.	Causalgia (upper extremity) following gunshot wound, with ulnar-radial palsy. Neurolysis contemplated.
19	M.S.	55	F	Radial N. palsy following trauma left upper ext. P.O.	1 mo.	5	2,450	Daily I.V.	Pain relief and greater mobility—sustained. Definite psychogenic element present.	Postoperative (hysterectomy), injury left brachial plexus, with causalgia and radial nerve palsy. Still under treatment.

* With tetra-ethyl-ammonium.

* With tetra-ethyl-ammonium.

TABLE II

SUMMARY OF THE RESPONSE TO TREATMENT WITH TETRA-ETHYL-AMMONIUM IN PATIENTS WITH POSTTRAUMATIC PAINFUL STIFFS

Case Name	Age	Sex	Initiating Factors or Etologic	Duration Symptoms	Number Autonomic Blocks*	Total Dose Milligrams	Duration Treatment	Result of Treatment and Duration of Benefit		Remarks	Follic in
								Complete sustained relief of pain	90% improvement in mobility. Minor tem- perature. Recurrence 4 months.		
1	E. W.	46	F	Multiple Trendelenburg pro- cedures ? Injury brachial plexus	6 mos	15	5 weeks Periodic I V.			? Injury brachial plexus Reflex sympa- thetic dystrophy. Causalgia pain, peri- arthritis	6 mos
2	D. L.	54	F	Old fracture of humerus	5 mos	15	8 weeks Periodic I V.			Old fracture—posttraumatic edema, in- tractable pain, periartthritis.	5 mos
4	M. M.	29	F	Unsupported "hanging cast." Operations both feet age 12	17 yrs	11	Periodic + 1 week daily I V.			Chronic Posttraumatic edema. with peri- odic vasospasm. Chronic posttubal teno- synovitis.	5 mos
6	R. B.	25	M	Old shrapnel wounds pop- liteal fossa Previous symp- toms and neurotomy.	18 days	5	Periodic 1 week I V.			Old shrapnel wounds popliteal fossa. ? Primary vasc. disease. Recurrent in- tractable pain	4 mos
9	O. K.	50	M	Open reduction ununited fracture Posttraumatic edema. with vasospasm and cyanosis.	3 days	3	Daily (3) I V.			Posttraumatic edema. with vasospasm following open reduction for ununited fracture.	3 mos
10	P. B.	35	F	Old trauma to ankle. ? Phlebitis, with vasospasm.	11 mos	4	Periodic I V.			Old trauma to ankle Intractable pain and swelling Vasospasm.	6 mos
11	H. H.	48	F	P. O. open reduction fore- arm. Vasospasm and edema	3 days	3	Daily I V.			Posttraumatic edema with vasospasm following open reduction forearm	7 mos
12	L. M.	54	F	Old malleolar fracture, with prolonged immobiliza- tion.	5 yrs	5	3 weeks Periodic I V.			Old tri-malleolar fracture. Traumatic arthritis Intractable pain and swelling.	5 mos
13	S. T.	53	F	Old fracture of elbow. Mul- tiple manipulations.	5 wks	3	3 days I V.			? Underlying Paget's disease, with patho- logic fracture. ? Myositis ossificans	6 mos
14	E. E.	65	M	Farm accident, with injury to shoulder.	4 mos	7	Daily 1 week I V			Brachial plexus injury. Fracture of spine of scapula. Sudek's atrophy of bone.	3 mos
15	R. C.	62	M	Old trauma to foot Pro- longed immobilization	9 mos.	1	1 day I V.			Posttraumatic painful state Further therapy advised.	
16	A. S.	48	M	Old Colles's fracture Im- mobilization.	4 mos	1	1 day			Post-traumatic painful state. Further therapy advised	
17	M. Z.	67	M	Old injury spine P. O. herniated nuc and neuroce- tomy.	7 yrs.	4	1 week I V.			Post-traumatic painful state. Further therapy advised.	6 mos
20	V. W.	60	F	Trauma left arm.	yrs	1	1 day I V.			Previous sympathectomy Minor causalgia with Sudek's atrophy of bone.	

* Tetra-ethyl-ammonium

M. L., white, female, age 59. Admitted to the Orthopedic Surgery Service (Dr. Carl Badgley), 2-16-'46, giving a history of having sustained a fracture-dislocation of the right elbow on 12-27-'45. Treatment had been carried out elsewhere and consisted of manipulation under anesthesia and plaster encasement. The day following this procedure, she had noted numbness in the thumb, index, and middle fingers in the right hand. At the end of two weeks in plaster encasement she had experienced considerable pain, edema of the hand, and difficulty moving the fingers. At the time of admission, 2-16-'46, the patient complained of burning pain radiating from the olecranon peripherally into the hand. Examination revealed hyperesthesia to touch, definite increase in sweating and trophic changes in the involved extremity. There was marked limitation of elbow motion, and the patient guarded the extremity carefully; a typical partial median nerve palsy was present. The patient had also required frequent doses of morphine to allay the pain. Relief of distress had also accompanied the use of wet bandages on the involved hand.

Injections of tetra-ethyl-ammonium, I. V. and I. M. were given daily, with definite relief of pain averaging five hours duration, total fractional dose 8,700 mg. Consideration was then given to resection of the head of the radius or dorsal sympathectomy being carried out. Because of the questionable presence of an early myositis ossificans, the patient was discharged home to return for further consideration in one month. She returned, 4-12-'46, at which time improvement was steady and pain was absent or slight. No operative intervention was deemed advisable. She returned again, 4-26-'46, showing considerable return of function in the involved arm and recurrence of pain in the elbow only. The original causalgic type pain had disappeared. Myositis ossificans was present in the area of fracture. Resection of the head of the radius was advised.

B. D., white, female, age 19. First seen in consultation, 2-4-'46, at which time the patient gave a history of having received a gunshot wound of the thigh one year previously (2-5-'45). The through-and-through wound was treated at a local hospital and healed uneventfully. The patient, however, complained of pain in the foot of an aching character, loss of control of the foot several days after operation, and experienced marked tenderness to pressure (attempted walking) and hypersensitivity to cold. An incomplete peroneal nerve palsy was present. Later, she developed moderate edema of the foot and limitation of ankle motion and was unable to bear weight on the extremity. The pain became persistent and increased slowly in intensity.

Examination on first admission revealed an incomplete peroneal palsy, atrophy of the lower leg, a moist cold foot which was tender on palpation, with some hyperesthesia of the skin around the ankle and dorsum of the foot. The patient could walk only with crutches and held the involved leg in a semiflexed position. A cyanotic reticular-livedo was present in involved extremity.

Tetra-ethyl-ammonium, 500 mg. I. V., produced a 4.5°C. rise in temperature of the toes bilaterally. The reticular-livedo immediately disappeared, and within a few minutes, all pain in the extremity ceased.

Because of the time interval which had elapsed since the initial trauma, lumbar sympathectomy was advised.

The patient was not seen again for several months (8-3-'46) at which time the tetra-ethyl-ammonium injection was again repeated, with similar results, and sympathectomy again advised. She returned to the clinic, 8-21-'45, at which time a program of daily sympathetic blocks utilizing tetra-ethyl-ammonium I. V. was instituted. Thereafter, nine such blocks were carried out, total fractional dose of 4,100 mg. being administered. The patient experienced immediate cessation of pain after each injection, pain relief gradually increasing to a point where it failed to return. The patient was ambulatory at this time. She was discharged pain-free and advised to return at intervals for follow-up examinations. Two weeks after discharge, a note from the patient reported that the pain recurred for brief intervals only, and that in general her condition was satisfactory.

E. D., white, female, age 48. The patient was first seen in the Department of Neurosurgery (Doctor Peet) on 8-5-'46. She gave a history of being well until 6-16-'44, at which time she sustained a minor injury to the second finger on the left hand when it was caught between a casting and guard on a rubber wheel. She was treated locally and continued working. Three days later the patient became aware of a stinging sensation in the distal phalanx which finally involved the entire finger. She was seen by the plant physician who splinted the finger and also started contrast baths, massage, manipulations, heat and roentgenotherapy. The pain continued to become more severe and changed to a burning-aching sensation, with diffusion and extension to hand, arm and shoulder. (The pain reached the shoulder approximately one year following the initial trauma.) Subsequently, the patient was examined by several physicians, all of whom concurred in a



FIG. 3.—A. Localized Sudek's osteoporosis associated with causalgia (December, 1944).

B. Roentgenographic findings in August, 1946. The osteoporosis is still largely confined to the phalanges of the middle finger.

diagnosis of psychoneurosis. Only one examining physician pointed out the numerous signs of causalgia present in the patient (severe burning pain, glossy skin, temperature changes, excessive sweating, hyperesthesia, and osteoporosis). This physician instituted local blocks and mecholyl ointment therapy. At the time of admission to the University Hospital the patient held the arm in a protected position, any contact being painful.

Examination revealed an obese female, demonstrating loss of joint motion particularly involving the wrist and fingers, shiny, glossy, atrophic skin on the hand, decreased temperature in the involved hand, hysterical clonus of the second finger and marked hyperesthesia. Roentgenologic examination and comparison with previous films brought by the patient (Fig. 3) demonstrated posttraumatic osteoporosis mainly confined to the 3rd left digit.

PERIPHERAL VASCULAR DISEASE

The patient was given daily injections of tetra-ethyl-ammonium—total fractional dose 8,500 mg.—17 injections. Definite relief of pain and obvious improvement in function gradually became demonstrable although the patient herself was loath to acknowledge (but did acknowledge) the benefits obtained. Although it was felt that sympathectomy would undoubtedly have relieved the patient, no surgical intervention was advised because of the irrevocable psychogenic element present. Periodic conservative therapy was therefore advised. Final diagnosis: causalgia-like pain with superimposed psychoneurosis. Localized Sudek's atrophy, peri-arthritis and fibrositis.

E. E., white, male, age 65. First seen in consultation, 8-13-'46, giving a history of having been run-over by a farm machine, 4-23-'46, at which time he sustained a bruised

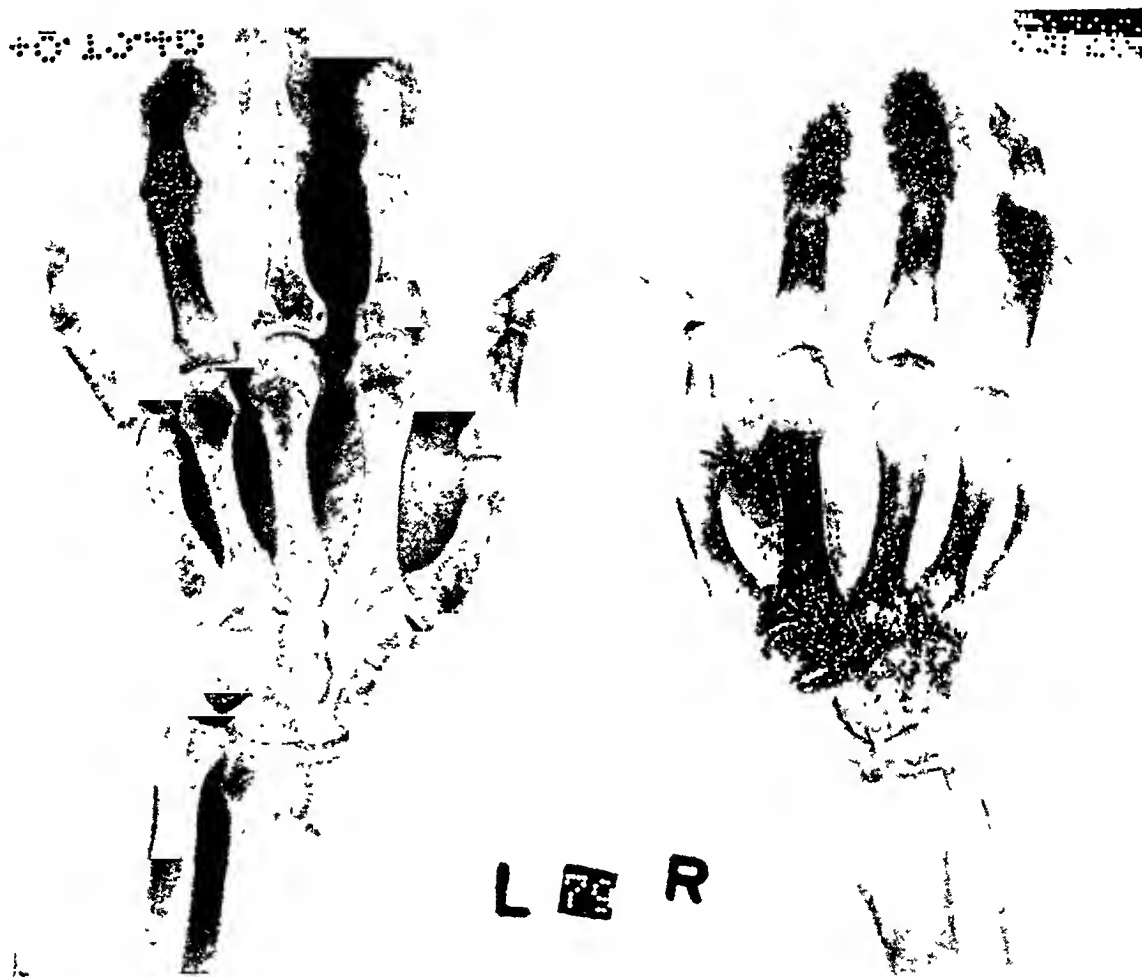


FIG. 4.—Marked osteoporosis of bones of the right hand and wrist following injury to shoulder four months previously.

right leg and right shoulder and a small laceration of the ear. Upon attempting to again run the machine, the patient fainted and the accident again recurred. He was placed at bed rest by his physician, the only complaint of the patient being periodic paresthetic shocks "like electricity" shooting down his right arm. Subsequently, the shoulder girdle and arm developed burning pain which increased in intensity. Because of this pain, joint motion was considerably impaired.

Examination revealed a tendency to winged-scapula, with questionable atrophy of the right infraspinatus muscle. The hand was thin and atrophic in appearance and hyperesthetic to touch. There was practically no scapulo-thoracic motion and the fingers were held in a partially flexed position. There was a $\frac{7}{8}$ -inch atrophy of the arm and a $\frac{5}{8}$ -inch atrophy of the forearm. Peri-arthritic edema and fibrosis was present in the hand.

Roentgenograms revealed generalized osteoporosis of the right shoulder girdle, hand and wrist, an old ununited fracture of the spinous process of the right scapula and an old healed fracture of the 5th metacarpal (Fig. 4).

The patient was treated with tetra-ethyl-ammonium to obtain a sympathetic block on seven occasions, (total fractional dose 3,500 mg.). He experienced immediate relief of pain, which gradually abated and eased following the course of therapy. The periarthritic edema and joint motion improved considerably and the patient was finally transferred back to the Orthopedic Service for manipulation of the various joints of the upper extremity under anesthesia, to attempt to lessen the ankylosis due to periarthritic fibrosis.

A summary of our experiences in treating patients with causalgia, and related posttraumatic painful states, is presented in Table IV. The history and clinical findings of these patients are listed in Table III. It will be noted that ten out of 20 cases had sustained relief of symptoms following repeated autonomic blockades with tetra-ethyl-ammonium. (Follow-up 2-6 months.) In general, however, such benefits in many instances were also related to periodic physiotherapy, which was carried out during the pain-free periods following autonomic blockades and which could only be carried out with difficulty at any other time. In the opinion of the authors, autonomic blockades which produce symptomatic relief in this group of patients does not remove the indications for appropriate sympathectomy. The use of tetra-ethyl-ammonium, however, at repeated intervals, has produced satisfactory results in certain patients in whom sympathectomy would have been desirable but was not felt to be feasible because of the presence of a marked psychogenic element or unstable personality.

Herpes Zoster and Postherpetic Neuralgia: Following the report by Findley and Patzer¹⁶ of the benefits derived from paravertebral procaine block in the treatment of herpes zoster, it was deemed advisable to attempt treatment of these patients by autonomic blockade with tetra-ethyl-ammonium (See Table V). Nine patients in this series were treated, therefore, with repeated injections of tetra-ethyl-ammonium usually at daily intervals. There were five males and four females, with an average age of 59 years (range 31-76). Five of these patients had postherpetic neuralgia, usually of long duration. The remaining four patients had acute or subacute herpes zoster. Each patient received an average of eight autonomic blocks with tetra-ethyl-ammonium (range 2-14) over an average period of 11 days. Three patients received intravenous and intramuscular therapy combined.

As a result of this therapy, 100 per cent of the patients obtained some relief of pain varying from a very brief period to six hours per block. The more sustained improvement occurred in the patients with acute or subacute herpes zoster and the least benefit was derived by those patients with old postherpetic neuralgia. This is in agreement with therapy carried out by paravertebral procaine blocks.

In general, younger patients responded better than older patients, although this was not invariably true. It was also noted that patients with herpes involving the cranial nerves were afforded the shortest interval of pain relief.

TABLE III

SUMMARY OF THE HISTORY AND CLINICAL FINDINGS IN 20 PATIENTS WITH CAUSALGIA AND VARIOUS POSTTRAUMATIC PAINFUL STATES

Case	Name	Age	Sex	Initiating Factors	Pain	Sensation Skin	Color Changes	Edema	Periarthritis and Fibrositis	Sweating	Atrophy	Osteoporosis	Diagnosis
1	E.W.	46	F	Injury brachial plexus.	Aching, burning	Hypers.	Waxy pallor	Moderate	Marked	Minimal	Minimal	Minimal	Reflex sympathetic dystrophy.
2	D.L.	54	F	Old fracture humerus.	Aching, burning	Hypers.	Waxy pallor	Marked	Marked	Minimal	Minimal	Marked	Reflex sympathetic dystrophy.
3	B.D.	19	F	Gunshot wound thigh.	Aching, burning	Hypers.	Blotchy livedo	Minimal	Moderate	Cold	Moderate	Causalgia.
4	M.M.	29	F	Bone surgery and encasements	Feet aching	Hypers.	Pallor flush	Marked	Minimal	Moderate	Minimal	Minimal	Posttraumatic edema.
5	E.D.	48	F	Crush injury finger.	Fingers aching	Hypers.	Waxy pallor	Moderate	Marked	Minimal	Moderate	Marked	Causalgia.
6	R.B.	25	M	Strapnet wounds.	Feet aching	Hypers.	Flush (infection)	Minimal	Moderate	Marked	Marked	Reflex sympathetic dystrophy.
7	L.L.	34	F	Chronic infection hand and forearm.	Hand-arm aching	Hypers.	Pallor cyanosis	Minimal	Marked	Moderate	Moderate	Marked	Causalgia. Drug addiction.
8	M.L.	59	F	Old fracture-dislocation.	Aching, burning	Hypers.	Pallor cyanosis	Moderate	Marked	Marked	Moderate	Moderate	Causalgia.
9	O.K.	50	M	Open reduction nonunion fracture	Mild	Pallor	Marked	Minimal	Marked	Posttraumatic edema.
10	P.B.	35	F	Old trauma to ankle.	Aching foot	Local hypers.	Livedo	Marked	Minimal	Moderate	Minimal	Reflex sympathetic dystrophy.
11	H.H.	48	F	Open reduction radius.	Aching fingers	Local hypers.	Marked cyanosis	Marked	Limited	Moderate	Moderate	Posttraumatic edema.
12	J.M.	54	F	Old trimalleolar fracture.	Painful foot	Bluish cyanosis	Marked	Minimal	Moderate	Posttraumatic edema.
13	S.T.	53	F	Old fracture elbow.	Aching arm	Hypers.	Glossy pallor	Marked	Moderate	Minimal	Marked	Traumatic arthritis. ?Reflex dystrophy.
14	E.E.	65	M	Injury to shoulder.	Aching, shooting arm	Hypers.	Waxy pallor	Moderate	Marked	Minimal	Marked	Marked	Reflex dystrophy. ?Paget's dis
15	R.C.	62	M	Old trauma to foot.	Burning ankle	Hypers.	Pallor, cyanosis	Moderate	Minimal	Moderate	Marked	Posttraumatic state.
16	A.S.	48	M	Old Colles's fracture	Burning hand	Hypers.	Waxy, erythema	Marked	Marked	Marked	Moderate	Marked	Posttraumatic edema.
17	M.Z.	67	M	Spine injury. P. O. Disc.	Burning heels	Normal	Moderate	Minimal	Minimal	Marked (old)	Marked	Posttraumatic state.
18	B.S.	53	M	Gunshot wound arm.	Tingling, aching	Hypers.	Glossy	Moderate	Marked	Marked	Marked	Marked	Posttraumatic state.
19	M.S.	55	F	Brachial plexus injury.	Burning, aching	Hypers.	Waxy pallor	Moderate	Marked	Marked	Marked	Marked	Causalgia.
20	V.W.	60	F	Trauma to arm.	Burning, aching	Hypers.	Waxy pallor	Minimal	Marked	Moderate	Minimal	Causalgia.
												Marked	Posttraumatic state. Previous sympathectomy.

Even so, many of these patients requested further therapy with tetra-ethyl-ammonium. In general, the response of the patient to the relief afforded by autonomic blockade with tetra-ethyl-ammonium was one of satisfaction or encouragement although it was recognized that in several of the older patients no permanent relief was being obtained.

The exact rôle played by vasospasm in patients with herpes zoster was difficult to interpret and further experience with this form of therapy will be necessary before any clear-cut decisions can be reached as regards the mechanism of pain relief by autonomic blockade. A summary of our experience in utilizing tetra-ethyl-ammonium in patients with herpes zoster and postherpetic neuralgia is presented in Table V.

TABLE IV
CAUSALGIA AND POSTTRAUMATIC PAINFUL STATES
STATISTICAL ANALYSIS OF TABLES I AND II

<i>Cases</i>	20
<i>Etiology or initiating factor.</i>	
Soft tissue trauma.....	11
Fractures.....	7
Unknown (P. O.).....	2
<i>Associated complete or partial nerve palsy</i>	5
<i>Duration of symptoms</i>	
Less than 1 month.....	3
More than 5 years.....	4
Average of 7 months.....	13
<i>Sex-incidence.</i>	
Females.....	13
Males.....	7
<i>Average age</i>	48
<i>Average number of ganglionic blocks</i>	7
<i>Average total dose of tetra-ethyl-ammonium (mg.)</i>	3,330
<i>Symptomatic relief—20 cases.</i>	
Temporary.....	6
Sustained.....	10
<i>Sympathectomy</i>	4
<i>No follow-up</i>	2
<i>Failures (tetra-ethyl-ammonium)</i>	2

FUNCTIONAL VASCULAR DISEASE

It was pointed out in a previous report⁵ on the effects of tetra-ethyl-ammonium on functional vascular disease that there was usually a marked response as regards blood pressure and rise in peripheral skin temperature (Fig. 2). The variation in duration of the response to autonomic ganglia blockade by tetra-ethyl-ammonium was pointed out. Further experience with this form of therapy in this group of patients has not modified the previously reported useful purposes of this form of ganglionic block in these patients: (1) the injection of tetra-ethyl-ammonium obviated the necessity of single or multiple paravertebral blocks; (2) it was helpful in demonstrating the presence of a functional vascular component especially in patients with scleroderma; and (3) it aided the establishment of a diagnosis. With further

PERIPHERAL VASCULAR DISEASE

SUMMARY OF THE TREATMENT OF PATIENTS WITH HERPES ZOSTER AND POSTHERPETIC NEURALGIA BY REPEATED AUTONOMIC BLOCKADE WITH TETRA-ETHYL-AMMONIUM

TABLE V

Num- ber	Name	Age	Sex	Duration	Location	Blocks	Total Dose (Mg.)	Period Treated	Response to Treatment	Diagnosis
1.	E.A.	73	F	Months	D ₆ -D ₇ and left arm post-herpetic neuralgia	6	2,150	6 days	Pain relief 1-4 hours per block, with nocturnal recurrence†	Postherpetic neuralgia
2.	A.S.	58	F	Weeks	Thoracic girdle pain. Residual lesions present					
3.	U.O.	76	M	Years	Postherpetic neuralgia	14	6,600	16 days	Ninety % improvement in two weeks—sustained.	Subacute herpes zoster
4.	J.F.	61	M	Years	D ₁₁ -D ₁₂ -L ₁	13	6,500	17 days	Improvement after second block. 50-75% sustained pain relief.	Postherpetic neuralgia
5.	S.P.	45	F	Days	Face, scalp and neck, right.	7	3,500	7 days	Temporary minimal relief of pain without definite improvement.	Postherpetic neuralgia
6.	A.M.	57	M	Years	Left occiput and postcervical area, severe, acute	11	5,500	16 days	Immediate relief of pain (6 hrs. per block). Un- sustained. Temporary improvement only.	Postherpetic neuralgia
7.	C.W.	55	M	Weeks	First division of trigeminal nerve	6*	4,100	12 days	Immediate relief of pain (6 hrs. per block). Un- sustained. Temporary improvement only.	Postherpetic neuralgia
8.	W.W.	76	M	Years	First and second divisions of trigeminal nerve	7*	4,800	14 days	Temporary improvement. Pain intensity de- creased and controlled with salicylates.	Acute herpes zoster
9.	D.S.	31	F	Days	D ₅ dermatome	9*	5,500	10 days	Temporary relief with each block. Chordotomy produced questionable relief.	Postherpetic neuralgia
					Herpes labialis of the perineum	2	750	2 days	Imm. relief pain 5-6 hrs. per block. Rapid sub- sidence	Acute herpes zoster

* Intravenous and intramuscular therapy combined.
† Paravertebral procaine block yielded identical results.

experience, the impression has been gained that tetra-ethyl-ammonium offers much to be desired as a therapeutic measure in these patients even when used at repeated intervals. Its diagnostic value is self-evident. Many of the patients with functional vascular disease have a marked sensitivity to their environment, *i.e.*, cold and psychic stimuli, and whereas the injection of tetra-ethyl-ammonium may produce a remarkable clinical alleviation of the vascular symptoms and picture, the factor of *time* intervenes, and with the disappearance of the ganglionic block, susceptibility to a recurrence of the attacks occurs. The injection of the drug has proven of value in fulminating functional vascular disease in our experience, and it is also our impression that in certain of the patients with Raynaud's phenomena, attacks have been aborted or modified in their intensity. With the exception of these circumstances, the utilization of tetra-ethyl-ammonium as a therapeutic measure has proven of little benefit. Our original impressions of its value as a diagnostic procedure have been greatly strengthened with added experience. It has in no sense replaced

TABLE VI

FUNCTIONAL VASCULAR DISEASE			
CLASSIFICATION OF PATIENTS WITH FUNCTIONAL VASCULAR DISEASE IN WHOM TETRA-ETHYL-AMMONIUM WAS USED AS A DIAGNOSTIC OR THERAPEUTIC MEASURE			
Raynaud's phenomena.....	16	Associated scleroderma.....	6
(primary and secondary)			
Livedo-recticularis.....	4	Disseminated lupus.....	1
Acrocyanosis.....	2		
Unclassified.....	7		
(environmental response)			
Pernio.....	1		
Total.....	30		

the value of sympathectomy in this group of patients. Table VI lists the classification of patients with functional vascular disease in whom tetra-ethyl-ammonium was used as a diagnostic or therapeutic measure.

ORGANIC OCCLUSIVE ARTERIAL DISEASE—BUERGER'S DISEASE

The opportunity of studying the effects of tetra-ethyl-ammonium in some 35 patients with thrombo-angiitis obliterans has been afforded within the past year. The average age of these patients was 40 years, and the average duration of symptoms five years, indicating an onset of the disease in most instances at age 35. There was only one female in the entire series. Fifty per cent of the patients were habitual smokers when first seen in the clinic. In the 35 cases, 71 extremities were involved and 40 per cent of the patients had an associated active or inactive superficial thrombophlebitis. Eight patients presented themselves initially either with a history of previous amputation (toe, foot, leg) or underwent some form of amputation subsequent to admission because of established gangrene or progressive suppurative infection. Diagnostic autonomic blockade alone was carried out in 16 of the 35 patients, largely for the

demonstration of any functional component that might exist. This particular group included those patients referred for diagnosis alone, patients with far-advanced occlusive arterial disease, or in whom infection or gangrene of a significant degree was already established and required more definitive therapy than autonomic blockade. In the remaining 19 patients, autonomic blockade with tetra-ethyl-ammonium was utilized both as a diagnostic and therapeutic measure, the latter largely to relieve vasospasm, if present, afford pain relief, improve claudication or aid in the amelioration of active superficial migratory thrombophlebitis. Tetra-ethyl-ammonium was utilized as a diagnostic measure in the sense of affording a prognosis of benefits to be derived were sympathectomy carried out. A total of ten lumbar sympathectomies was performed in this series of patients. Nine of these were carried out on the basis of the response to autonomic blockade with tetra-ethyl-ammonium. Therapy with repeated autonomic blockades, utilizing tetra-ethyl-ammonium was carried out in eight of the 19 patients for pain alone, in seven patients for claudication

TABLE VII
THROMBO-ANGIITIS OBLITERANS
THE RESULTS OF THERAPY WITH TETRA-ETHYL-AMMONIUM IN PATIENTS WITH
THROMBO-ANGIITIS OBLITERANS

	Cases	Early to Mod. Advanced	Far-advanced or Terminal
Relief of pain..... (temporary or sustained)	12	8	4
Improvement in claudication.....	11	11	0
Active phlebitis.....	4	3	1

	Functional Component Present (Vasodilation-Vasoconstriction)		Absent
Relief of pain.....	12	10	2
Improvement in claudication.....	11	10	1

unassociated with severe rest or nocturnal pain, and in four patients with symptoms of pain and claudication combined. Four of these patients also presented themselves with active superficial migratory phlebitis. In the series of patients with Buerger's disease treated with repeated intravenous injections of tetra-ethyl-ammonium—each patient received an average of six autonomic blocks, (range 2–18), usually given at daily intervals, but in some instances at longer intervals largely dependent upon the response of the patient to this therapy in conjunction with other conservative measures, and the availability of the patient for treatment. The results of treatment in this manner as regards relief of pain and claudication are illustrated in Table VII.

In the nine patients in this series who underwent lumbar sympathectomy on the basis of their previous response to tetra-ethyl-ammonium, 100 per cent achieved results classified as good to excellent, *i.e.*, if pain had ceased following a test dose of tetra-ethyl-ammonium, or if a functional component had been

previously demonstrated by the thermocouple measurements and visible clinical improvement, similar results were achieved with sympathectomy as predicted by the response of the patient to tetra-ethyl-ammonium. In those patients available for postoperative study, the skin temperature response to sympathectomy under like conditions of room temperature was found to be amazingly identical to the recordings made preoperatively following injection of tetra-ethyl-ammonium.

Table VII illustrates graphically the relationship of the presence or absence of a functional component and the severity of the disease process to the results obtained in patients with thrombo-angiitis obliterans treated by autonomic blockade. It will be noted that patients with an early to moderately advanced process experienced significant improvement either in severity of their pain or amelioration of their claudication. None of the far-advanced or terminal cases had improvement in claudication with this therapy. If a functional component was established, some benefit was derived from autonomic blockade in most instances. It is of interest to note, in addition, that some of the cases first treated successfully in this manner have sustained their improvement over a 12-month period, without reactivation of their disease process. This is not entirely due, of course, to therapy with autonomic blockade alone.

Certain definite impressions have been derived from treating this series of patients with thrombo-angiitis obliterans by repeated autonomic blockades with tetra-ethyl-ammonium. They are as follows:

1. The response to the injection of the drug (either plethysmographic response or skin-temperature recordings with a thermocouple) can be utilized as an excellent gauge of the degree of occlusion and collateral circulation in the arterial vessels of the extremities (Figs. 1 and 2).

2. The response to the injection of the drug has been found reliable when used to predict the response in the involved extremities to appropriate sympathectomy.

3. Tetra-ethyl-ammonium has afforded relief of pain in numerous instances, particularly rest pain, and in some cases irrespective of the presence of a functional component or vasospasm. The cessation of pain, following injection of the drug, has at times been extremely rapid. Pain relief has at times been temporary and at times sustained, particularly if therapy is repeated at appropriate intervals. The duration of relief of pain has borne no fixed relationship to duration of autonomic block.

4. The injection of tetra-ethyl-ammonium is followed by visible, palpable and measurable relief of vasospasm when such is present clinically.

5. The injection of the drug has been of no avail in the presence of severe infection or established gangrene in this series of patients.

The following case reports are presented to illustrate in Case H. M. the improvement in claudication and pain following a three-week period of daily autonomic blockades, and Case E. B. to illustrate a bizarre, yet highly satisfactory control of intractable pain in a patient with far-advanced thrombo-angiitis obliterans and drug addiction.

CASE REPORTS

H. M., age 29, Jewish male, first seen in the Surgery Clinic on 10-8-'46. The patient was in excellent health until December, 1945, at which time he began to experience pain in his calves of a spontaneous nature and not aggravated by exercise. Two weeks later he noted the onset of pain in his hands and subsequently observed the development of numbness, coldness and cyanosis of the toes and fingers. He was seen at another clinic in August, 1946, at which time a "thrombosed vein" was excised from the superficial area of his calf. He gave a history of smoking one-half to one package of cigarettes daily, and the occurrence of night pains in his calves and feet. There had been a recent development of intermittent claudication (2 blocks).

On physical examination, findings of note were limited to the lower extremities. In the right foot, the posterior tibial pulse was absent and there was an aberrant dorsalis pedis pulse present along the lateral malleolus. In the left foot, the dorsalis pedis pulse was absent, the posterior tibial pulse was palpable. Elevation of both legs produced a cyanotic mottling and marked pallor of the right great toe. The venous filling time of the right foot was sluggish as compared to the left foot. Dependency produced a cyanotic rubor of the right great toe. Thermocouple studies revealed a temperature gradient of 7.2°C. on the right leg and 7.8°C. on the left leg.

The patient was given 500 mg. of tetra-ethyl-ammonium chloride intravenously. Thirty minutes later, no rise in temperature had occurred in the right lower extremity and a 4°C. rise in temperature had occurred in the left foot.

From the history, physical findings, and response to autonomic blockade a diagnosis of thrombo-angiitis obliterans was made. A functional component on the left leg and organic occlusion in the right leg was demonstrated.

Thereafter the patient received a series of 16 daily intravenous injections of tetra-ethyl-ammonium chloride to produce a sympathetic block. *These were administered by his own physician.* He returned, 11-8-'46, one month after having first been seen in the clinic. At that time, practically all claudication had ceased, the patient was experiencing no night pains and he expressed the opinion that his condition was 95 per cent improved. He was advised to return at intervals for reexamination.

E. B., age 43. The patient had been seen at the University Hospital at intervals over a period of several years. In 1943 he had developed typical intermittent claudication and rest-pain in his extremities. These symptoms had gradually increased in severity to the point of invalidism from constant pains. A diagnosis of thrombo-angiitis obliterans was made in December, 1943, the most active process being in the left lower extremity.

Left lumbar sympathectomy was carried out subsequently in June, 1944. During this operative procedure the left ureter had been injured and a left nephrectomy was ultimately necessitated in August, 1944. Convalescence was satisfactory and all pain in the left lower extremity had ceased.

The patient inadvertently injured the right great toe in November, 1944, and a supracondylar amputation was carried out elsewhere for established gangrene.

The patient returned to the Surgery Clinic, 8-19-'46, in a state of chronic invalidism and drug addiction (dilaudid). He was suffering from a bizarre distribution of severe pain of a constant nature involving the stump of the amputated limb, the site of the nephrectomy scar, and the site of the sympathectomy scar. There was also a recurrence of the burning pain in the left lower extremity (previously sympathectomized). The patient had been receiving dilaudid gr. $\frac{1}{16}$ q. 3 h., day and night, for the previous three months in an effort to relieve his painful state.

The essential findings in the physical examination were extremely sensitive, tender scars in the left flank, pain on light pressure over the scar in the amputation stump, and absence of all pulses in the left lower extremity, with the exception of the femoral pulse. The clinical impressions were: (1) Thrombo-angiitis obliterans, with severe ischemic

neuritis; (2) drug addiction (dilaudid); (3) phantom limb pain; (4) postoperative neuralgia (sears); and (5) psychoneurosis.

Inasmuch, as the history and physical findings pointed to a far-advanced occlusive arterial disease and because sympathectomy had been carried out previously, and drug addiction was now present, it was not considered that much aid could be given the patient from a series of autonomic blockades. The patient was hospitalized, however, and a series of eight injections of tetra-ethyl-ammonium I. V. carried out. A total dose of 4,000 mg. was administered in a one-week period. During this interval all narcotic medication was stopped and the patient successfully endured the expected withdrawal symptoms. Marked alleviation of pain was noted following the fourth sympathetic block. The bizarre pains were gradually lessened in intensity and finally disappeared. The personality change in the patient was remarkable. He stated that he now felt better than he had for several years. The patient became ambulatory on crutches, and was discharged home without medication.

The conversion of a "basket-type" case of terminal Buerger's disease, with drug addiction, into a pain-free ambulatory patient, in whom analgesics were unnecessary, as a result of repeated autonomic blockades was difficult to reconcile. The case is reported, however, to emphasize the possibility that the autonomic nervous system may be important from other standpoints than vasospasm alone, in patients with vascular disease. It was also considered that, inasmuch, as the patient tolerated the withdrawal of large amounts of dilaudid, that pain had actually been present and had ceased with the therapy given.

PERIPHERAL ARTERIOSCLEROSIS OBLITERANS

To date, approximately 125 patients with peripheral arteriosclerosis obliterans have received tetra-ethyl-ammonium as a diagnostic, prognostic or therapeutic measure. In a previous report⁵ it was pointed out that the drug had proven useful in two respects in these patients: (1) aiding in the control of nocturnal pain; and (2) as an index of the possible benefits that might be derived from a lumbar sympathectomy. The experience gained since the original report has done nothing to modify the impressions previously obtained other than to fortify them. The occasional arteriosclerotic evidences a rather surprising improvement in claudication following autonomic blockade with tetra-ethyl-ammonium, but it should be emphasized that this is not the usual experience with this group of patients. The injection of the drug, will, of course, not modify established gangrene. The occasional patient with arteriosclerosis obliterans demonstrates a surprising degree of functional response (vasodilatation) following the injection of tetra-ethyl-ammonium. For this reason, all patients with symptomatic peripheral arteriosclerosis are tested accordingly, since, in our experience, such patients demonstrate marked benefits from lumbar sympathectomy. On the other hand, lack of response to the drug is not a contraindication for operation (sympathectomy) primarily, because the factor of *time* is not taken into consideration. Given sufficient time, following lumbar sympathectomy, many arteriosclerotics evidence satisfactory improvement despite an absence originally of any demonstrable functional component or response to sympathetic block, autonomic block, or spinal anesthesia (Fig. 2). This impression has been gained from observations on 40 lumbar

sympathectomies in patients with peripheral arteriosclerosis obliterans—many of whom have now been followed over a considerable time-interval.

Certain dangers inherent to the administration of tetra-ethyl-ammonium in this group of patients are discussed under the section in this paper describing toxic effects.

THROMBOPHLEBITIS

Tetra-ethyl-ammonium has presented an excellent clinical tool for evaluation of therapeutic benefits to be obtained from autonomic ganglion blockade in thrombophlebitis.^{17, 18} Twenty-six cases of thrombophlebitis, in all stages of its progression, have received tetra-ethyl-ammonium either as a therapeutic procedure or in an attempt to evaluate the degree of vasospasm present. Five patients received only one injection as part of their diagnostic work-up. The remaining 21 patients have received two or more injections as a definitive therapeutic measure. Twenty-one cases have been classified as chronic, four as subacute, and one as acute, based upon the duration of their symptoms and physical findings. Edema of some degree was present in all patients treated, as was pain or leg discomfort. Vasospasm was identified in 52 per cent of the treated cases, as manifested by hyperhidrosis, pain, mild cyanosis, coldness and demonstrable vasoconstriction.

Excellent response to repeated autonomic ganglion blockade was observed in the one acute case and in three treated cases of subacute thrombophlebitis. Marked pain relief occurred in a matter of hours and in a few days there was little, if any, residual edema.

Individuals suffering from the resultant effects of chronic thrombophlebitis noted subsidence of edema, relief from congestive pain and a new sense of well-being, as regards the involved extremity. Relief of vasospasm was welcomed by those who, for many years, had been distressed by a cold, moist limb. The duration of the response to ganglionic block was variable, at times extending over a period of days, or longer. Occasionally the benefits derived were of brief duration.

It is of interest to note that in a separate study of chronic thrombophlebitis in 100 patients whose cases were chosen at random from the code room of the hospital, 81 returned at an average interval of 2–3 years following the onset of their disease complaining of pain. Ninety-one of 96 recorded findings in the 100 cases demonstrated edema, and pain and edema were present together in 76 of 96 records of symptomatology. The benefits derived from periodic autonomic blockade with tetra-ethyl-ammonium, while in no sense curative, afforded sufficient temporary relief from pain and edema in these patients to provide a highly satisfactory interval-form of therapy. The patients with deep chronic thrombophlebitis were, for the most part, highly pleased with this form of treatment despite its recognized limitations.

Table VIII is self-explanatory in the listing of symptoms present, duration of the disease and response to autonomic blockade in 21 patients with thrombophlebitis in all the stages of its progression. The five remaining patients received diagnostic blockade only, with a single injection.

TABLE VIII
TUROMBOPHLEBITIS
SUMMARY OF THE CLINICAL HISTORY, SIGNS AND SYMPTOMS AND RESPONSE TO TREATMENT OF PATIENTS WITH TUROMBOPHLEBITIS

Num- ber	Name	Age	Sex	Duration of Sym- ptoms	Extrem- ity In- volved	Edema	Pain	Derna- titis	Pigmen- tation	Ulcera- tion	Vaso- spasm	Treat- ment	Total Dosage (Mg.)	Impressions
1.	W.L.	45	M	6 wks.	R. leg	Marked	Mod.	14	7,000	Marked diminution of pain in 48 hours; complete subsidence of edema in 4 days
2.	M.M.	53	F	9 mos.	Both legs	Mod.	Marked	13	6,500	Symptomatic relief of pain for long periods of time; edema controlled with elastic support.
3.	L.B.	44	F	26 yrs.	L. leg	Marked	Min.	Mod.	11	5,500	Satisfactory improvement of both pain and edema; symptomatic relief of tiredness and heaviness.
4.	E.M.	36	F	20 yrs.	Both legs	Marked	Mod.	Min.	Mod.	Marked	9	4,500	Excellent relief of subjective symptoms; edema subsided and controlled with elastic support.
5.	L.T.	55	F	30 yrs.	L. leg	Marked	Mod.	Mod.	Marked	Mod.	9	4,500	Moderate improvement in edema and pain; no improvement in ulceration during limited period of treatment.
6.	C.R.	49	M	6 wks.	L. arm	Min.	Mod.	9	4,500	Complete subsidence inflammatory process left arm; no recurrence to date.
7.	R.G.	22	M	4 yrs.	Both legs	Marked	Mod.	Mod.	Marked	Marked	Mod.	11	5,500	Complete resolution of edema and controlled with elastic support; all ulcerated areas healed well.
8.	T.E.	31	M	4 mos.	L. leg	Marked	Marked	8	4,000	Complete subsidence of edema in 7 days controlled with elastic support; rapid improvement pain and temperature.
9.	M.W.	31	F	5 yrs.	L. leg	Mod.	Mod.	Min.	Marked	8	4,000	Leg less painful; edema subsiding slowly; moderate relief of ease of fatigue of leg.
10.	H.M.	45	F	20 yrs.	Both legs	Mod.	Mod.	Mod.	Marked	6	3,000	Legs no longer ache; rest pain gone; edema is improved.
11.	M.S.	30	F	5 yrs.	L. leg	Mod.	Mod.	Marked	4	2,000	Periods of edema less often and severe; excellent relief of vasospasm; subjective improvement.

TABLE VIII—Continued
SUMMARY OF THE CLINICAL HISTORY, SIGNS AND SYMPTOMS AND RESPONSE TO TREATMENT OF PATIENTS WITH THROMBOPHLEBITIS

Num- ber	Name	Age	Sex	Duration of Sym- ptoms		Extrem- ity In- volved	Edema	Pain	Derma- titis	Pigmen- tation	Ulcera- tion	Vaso-Treat- ment	Total Dose (Mg.)	Impressions	
12.	R.S.	20	F	24 hrs.	L. arm	Marked	Marked	Marked	4	2,000	Marked subsidence of pain and edema in 24 hours; venous pressure remained high, however, at time of discharge from hospital.
13.	P.B.	35	F	11 mos.	R. leg	Min.	Marked	Marked	Marked	4	2,000	Old calf vein thrombosis secondary to injury; immediate relief of pain after injection; subsequent lumbar sympathectomy produced complete alleviation of symptoms.
14.	K.D.	28	F	5 yrs.	L. leg	Mod.	Min.	Min.	Marked	3	1,500	Edema subsiding; leg less tired and congestive pain has improved; vasospasm not as severe.
15.	B.C.	56	M	6 mos.	L. leg	Marked	Mod.	Mod.	Marked	5	2,500	Marked reduction in swelling and congestive pain; severe coronary infarct necessitated cessation of treatment. Subsequent death from coronary thrombosis.
16.	F.D.	52	F	20 yrs.	L. leg	Marked	Mod.	Mod.	Mod.	Mod.	Marked	Marked	3	1,500	Subjective improvement; edema less marked; observation period to date too short to observe improvement in ulcerations.
17.	E.H.	46	F	2 yrs.	Both legs	Mod.	Mod.	Mod.	Mod.	Mod.	2	1,000	Postoperative ligation of the vena cava which developed subsequent static dermatitis and ulceration; subjective improvement of congestive pain.
18.	A.V.	25	F	2 yrs.	R. leg	Mod.	Marked	Marked	Mod.	2	1,000	Pain persists; subjectively the leg is improved as regards heaviness and ease of fatigue.
19.	A.F.	54	F	8 mos.	R. leg	Mod.	Marked	Marked	5	2,500	Pain persisted, but there was subsidence of edema; onset of swelling, followed high saphenous ligation.
20.	C.N.	43	M	3 yrs.	R. leg	Min.	Mod.	Mod.	4	2,000	Symptomatic relief and subsidence of superficial phlebitis (Buerger's disease).
21.	L.S.	51	F	1 yr.	L. leg	Min.	Mod.	Mod.	Marked	Marked	Mod.	Mod.	2	400	Symptomatic relief and relief of vasospasm.

Of the 21 cases in Table VIII, the duration of symptoms varied from one day to several years. The vast majority of these patients had chronic thrombophlebitis. An average of seven autonomic blocks was given to this group of patients, the usual intravenous dose ranging from 250-500 mg. This therapy, for the most part, was given periodically.

UNDESIRABLE REACTIONS TO TETRA-ETHYL-AMMONIUM

The administration of tetra-ethyl-ammonium in dosages of 500 mg., or less, has not been accompanied by any serious toxic effects in more than 1,500 injections. One patient has received 42,000 mg. over a period of six weeks without unfavorable sequelae. Caution must be exercised in giving this drug to certain types of patients however. Hypertensive patients, particularly those in whom a neurogenic component of the hypertension has been identified or suspected, should have great care exercised during administration. Precipitous drops in blood pressure have been encountered in these patients, the systolic pressure falling as low as 50 mm. of mercury. Nausea, vomiting, sweating, pallor, and temporary peripheral circulatory collapse are concomitant with this marked fall in pressure. Nonhypertensive patients, in whom it is reasonable to anticipate an overly-labile sympathetic nervous system, should also have the drug administered with caution. Elderly patients, as a rule, do not tolerate tetra-ethyl-ammonium as well as the younger age-groups. It is advisable, in older individuals, to start with small dosages and gradually work up to 500 mg. over a period of a few days. Undesirable falls in blood pressure may be quickly and effectively countered by a moderate Trendelenberg position and injection of a few minims of epinephrine.

A state of dyspnea similar to that observed in hysterical hyperventilation has developed in some patients immediately after injection of tetra-ethyl-ammonium. In a few patients the sensation of weakness, fatigue and lightheadedness was very pronounced. They appear to experience difficulty with muscle movement, though when tested there was no loss of strength or change in reflexes.

A delayed drop in blood pressure has been observed in certain patients, usually in the older age-group, who, after partial return to normal of the initial drop in pressure, apparently lose their compensating mechanisms defending blood pressure and a secondary drop in pressure takes place which may be greater than the primary fall. Again, undesirable falls in blood pressure may be countered by the above measures.

Some patients treated daily over a long period of time, develop a mild degree of myasthenia and lassitude that disappears with cessation of administration of the drug. Occasionally, a patient has noted difficulty in urination during active treatment, especially when intramuscular injection has been employed. It is, of course, inadvisable to administer tetra-ethyl-ammonium in anuric states as its excretion is largely dependent upon adequate renal function.

In small patients a 500 mg. I. V. injection may be followed by fasciculation of muscles. This is probably evidence of over-dosage. Large intramuscular doses in obese people may produce the same effect which may last for several hours. No ill effects have been noted from this phenomena.

DISCUSSION.—Autonomic blockade, in a patient with vascular disease or related disorders, which produces alleviation of pain or amelioration of the clinical picture, may produce such an effect by means other than relief of vasospasm alone. The exact mechanism involved is unknown. It is postulated by the authors that many of the results observed in the several series of cases reported in this paper might best be explained upon the basis of altered tissue metabolism secondary to sympathetic block or sympathectomy, realizing, of course, that in certain cases, altered blood flow secondary to the procedures mentioned might, in turn, produce desirable alterations in tissue metabolism which were in turn reflected as modifications or improvement in the clinical picture. Such a postulation was primarily necessitated by numerous observations of marked symptomatic improvement occurring in patients with vascular disease in whom vasodilatation was not produced by autonomic blockade. The possibility of a vicious reflex arc being interrupted by ganglionic block with subsequent modification of the pain mechanism must of course be given due consideration. If such actually occurs, it still leaves unexplained the duration of relief of symptoms far-outlasting the expected duration of the block. This frequently seen phenomena, again, suggests modified tissue metabolism of an unknown nature. It is also possible that certain afferent pathways (if such exist) in the autonomic nervous system may be blocked by the injection of tetra-ethyl-ammonium and, thus, contribute to the relief of painful symptoms.

SUMMARY

1. The administration of tetra-ethyl-ammonium for the production of autonomic blockade has proven of value in diminishing or relieving in severity the pain of causalgia, posttraumatic painful states, herpes zoster, Buerger's disease and thrombophlebitis. The improvement following such therapy has been sustained in certain cases.
2. The drug has proven to be a satisfactory implement for clinical investigation and therapy in the conditions reported.
3. The occurrence of certain undesirable side-effects following the administration of tetra-ethyl-ammonium in some cases necessitates the institution of certain precautions during its administration.

BIBLIOGRAPHY

- ¹ Acheson, G. H., and Moe, G. K.: Some Effects of Tetra-ethyl-ammonium on the Mammalian Heart. *J. Pharm. and Exp. Therap.*, **84**, 189, 1945.
- ² Acheson, G. H., and Moe, G. K.: The Action of the Tetra-ethyl-ammonium Ion on the Mammalian Circulation. *J. Pharm. and Exp. Therap.*, **87**, 220, 1946.
- ³ Lyons, R. H., Moe, G. K., Campbell, K. N., Neligh, R. B., Hoobler, S. W., Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man: Preliminary Observations on the Use of Tetra-ethyl-ammonium Bromide. *University Hosp. Bull.* **12**, 33, April, 1946.
- ⁴ Lyons, R. H., Moe, G. K., Neligh, R. B., Hoobler, S. W., Campbell, K. N., Berry, R. L., and Rennick, B. R.: The Effects of Blockade of the Autonomic Ganglia in Man with Tetra-ethyl-ammonium: Preliminary Observations on its Clinical Application. *Am. J. Med. Sci.*, **213**, 315, March, 1947.
- ⁵ Berry, R. L., Campbell, K. N., Lyons, R. H., Moe, G. K., and Sutler, M. L.: The Use of Tetra-ethyl-ammonium in Peripheral Vascular Disease and Causalgic Disorders. *Surgery*, **20**, 525, October, 1946.

- ⁶ Lapides, J., Nesbit, R. M., Valk, W. W., Sutler, M. L., Berry, R. L., Lyons, R. H., Campbell, K. N., and Moc, G. K.: The Effect of Autonomic Blockade on the Urinary Bladder in Man. *J. Urology*, 57, 242, February, 1947.
- ⁷ deTakats, G.: Reflex Dystrophy of the Extremities. *Arch. Surg.*, 34, 939, 1937.
- ⁸ Evans, J. A.: Reflex Sympathetic Dystrophy. *Surg. Gynec. and Obst.*: 82, 36, 1946.
- ⁹ Mahorner, H.: Sympathetic Nerve Blocks in Rehabilitation of the Injured Extremity. New Orleans M. and S. J., 94, 426, 1941-1942.
- ¹⁰ Atlas, L. N., Traumatic Vasospastic Dystrophy of the Extremities. *Arch. Surg.*, 42, 1042, 1941.
- ¹¹ Leriche, R.: Surgery of Pain (Translation by Archibald Young). William and Wilkins Co., Baltimore, 1939.
- ¹² Allbritten, F. F., Maltby, G. L.: Causalgia Secondary to Injury of the Major Peripheral Nerves. Treatment by Sympathectomy. *Surgery*, 19, 407, 1946.
- ¹³ Wolff, H. G., Cattell, M.: Effect of Stimulation of Sympathetic and Dorsal Roots on Contraction of Skeletal Muscle. *Arch. Neurol. and Psychiat.*, 32, 81, 1934.
- ¹⁴ Corkell, A. B., Marks, H. P., Soskin, S.: The Effects of Sympathetic Stimulation and of Adrenaline on Muscle Glycogen. *J. Physiol.*, 83, 26, 1934-1935.
- ¹⁵ Doupe, J., Cullen, C. H., Chance, G. Q.: Posttraumatic Pain and the Causalgic Syndrome. *J. Neurol., Neurosurg., and Psychiat.*, 7, 33, 1944.
- ¹⁶ Findley, T., Patzer, R.: The Treatment of Herpes Zoster by Paravertebral Procaine Block. *J. A. M. A.*, 128, 1217, August 25, 1945.
- ¹⁷ Ochsner, A., DeBakey, M.: Peripheral Vascular Disease: A Critical Survey of its Conservative and Radical Treatment. *Surg. Gynec. and Obst.*, 70, 1058, 1940.
- ¹⁸ Ochsner, A., DeBakey, M.: Therapeutic Considerations of Thrombophlebitis and Phlebothrombosis. *New England J. Med.*, 225, 207, August, 1941.
- ¹⁹ White, J. C.: Diagnostic Blocking of the Sympathetic Nerves to the Extremities with Procaine. *J. A. M. A.*, 94, 1382, 1930.
- ²⁰ Neligh, R. B., Holt, J., Lyons, R. H., Moc, G. K., and Hoobler, S. W.: The Effect of Blockade of Autonomic Ganglia by Tetra-ethyl-ammonium in the Gastro-intestinal Tract in Man. In press.

DISCUSSION.—DR. WILLARD BARTLETT, St. Louis, Mo.: I should like to ask the duration of the effect, and how frequently injections are needed.

DR. MICHAEL E. DEBAKEY, New Orleans, La.: At the present time Drs. Thorpe Ray, George E. Burch, and I are engaged at the Tulane University School of Medicine in a study of vascular responses to tetra-ethyl-ammonium bromide, in an effort to evaluate its practical usefulness in peripheral vascular problems. The physiologic and clinical aspects of these studies will be described later. The observations upon which the following comments are based are not considered sufficiently extensive to permit a final evaluation of this agent, but the great interest manifested in its use, the consistency of the data, and the definite differences between our findings and those of other observers prompt this preliminary report.

In addition to clinical observations, objective studies have been made of the peripheral vascular response to tetra-ethyl-ammonium bromide by means of plethysmographic and thermometric measurements on normal subjects and on patients with peripheral vascular disease. These studies were made under controlled atmospheric conditions, after the intravenous administration of 300 to 500 mg. of tetra-ethyl-ammonium bromide, first under resting conditions and then following local nerve and regional sympathetic block.

As will be noted from the graphs presented, the clinical or general systemic reactions to the drug were essentially similar to those reported by others, though much less pronounced and of much shorter duration. The plethysmographic and thermometric data, however, were quite different. Following the administration of tetra-ethyl-ammonium bromide there was a variable response in skin temperature as determined at 11 to 20 different areas, varying from no response at all in some instances to a maximum rise of

4° C. in others. In a few areas there was an actual decrease in the skin temperature. If an elevation occurred, it did not persist more than 15 minutes in any case.

After a return to the basal vascular status, local nerve and regional sympathetic block invariably produced an increase in the skin temperature from two to six times greater than the increase caused by tetra-ethyl-ammonium bromide. Of particular significance is the fact that local nerve or regional sympathetic block invariably resulted in an increase in skin temperature in areas which had failed to respond to the use of the drug. Finally, the duration of the elevation following local nerve or regional sympathetic block was in every instance considerably more prolonged than the elevation following the use of the drug.

Measurements by plethysmography, which is an extremely sensitive and rapid method of study, were made simultaneously with the thermometric determinations and invariably corroborated the thermometric observations for the tips of the fingers and toes. The percentage change, in fact, was shown to be even greater, and it occurred without any lag.

We have no explanation for the distinct differences between these results and those reported by others. On the basis of our own observations, however, it seems unlikely that tetra-ethyl-ammonium bromide will prove of great value, either diagnostically or therapeutically, in peripheral vascular disease.

DR. DANIEL C. ELKIN, Emory University, Ga.: An investigation of the use of tetra-ethyl-ammonium bromide in cases of acute arterial injuries has been progressing in the surgical laboratory of Emory University Medical School under the direction of Drs. F. W. Cooper, Jr., and R. L. Robertson. The method has consisted of excising the trifurcation and terminal portion of the aorta in dogs. At the time of operation and postoperatively the dogs received a varying number (six to nine) of injections of tetra-ethyl-ammonium bromide in the amount of 25 mg. per kilogram of body weight.

It has been previously shown by Brooks, Leriche and others that excision of the bifurcation of the aorta without sympathectomy will result in swelling, paralysis, gangrene and death in the majority of animals. A group of control animals was run with confirmation of these findings in every instance. Ten animals have been similarly operated upon, but in addition received tetra-ethyl-ammonium bromide. None of these animals developed swelling, ulcerations or gangrene of the posterior extremities. A transient weakness was present in all instances, but in the dogs which survived this cleared within four days. Through technical error the intramuscular injections were given in the posterior extremity in one instance, with the formation of an abscess, and with the dog dying on the 9th postoperative day as a result of extensive suppuration.

The marked clinical improvement in the nine animals which survived with rapidly increasing tolerance for activity, suggests that tetra-ethyl-ammonium bromide may be a valuable adjunct in the treatment of acute arterial injuries of major vessels.

DR. R. L. BERRY, Ann Arbor, Mich.: In reply to Doctor Bartlett's question, the block reached a maximum height between 20 and 30 minutes, and gradually tapered-off to depletion usually in 60 to 80 minutes, as manifested by thermacouple response.

DR. FREDERICK A. COLLIER, Ann Arbor, Mich. (closing): I want to thank Doctors DeBailey and Elkin for their discussion. I think there can be no doubt about the pharmacologic action of the drug that has been carefully worked out by Doctor Acheson and Doctor Moe, and their associates.

The observations of Doctor DeBailey that tetra-ethyl-ammonium bromide does not cause the degree of vasodilation produced by lumbar block is interesting, but not at all in accord with our observations, which have been many. I shall await with interest to learn of his further experiences with this chemical.

There is so much that we do not yet know about the autonomic nervous system, but we feel that this chemical method of study may be helpful in adding to our knowledge of that system, as well as offering a new therapeutic measure for the relief of unpleasant symptoms associated with its disorders.

WOUNDS OF THE LIVER*

J. D. MARTIN, JR., M.D.

ATLANTA, GA.

FROM THE DEPARTMENT OF SURGERY, EMORY UNIVERSITY, GEORGIA

LIVER WOUNDS occur with such frequency and severity that they may be considered the major problem in abdominal injuries. Fox¹ reviewed 270 thoraco-abdominal wounds seen in an American hospital in Italy, and reported a 57 per cent involvement of the liver. In approximately 10 per cent of these there was an associated injury of other viscera. The over-all mortality rate for wounds of the liver was 27 per cent in 829 patients, according to Madding.²

The liver, the largest organ in the body, is extremely vulnerable to penetrations of both lower chest and upper abdomen. It should be emphasized that the liver is an organ with multiple functions and that as the result of trauma various manifestations occur which may or may not be related to the severity of the trauma. Experimental removal³ of as much as 50 per cent of hepatic tissue can be performed without serious impairment of function. It has been demonstrated that the liver has remarkable regenerative and recuperative power.⁴ In dogs, as much as 90 per cent of the liver can be removed at successive intervals with survival of the animal, and, following massive blood loss,⁵ the functional reserve has been shown to be unimpaired.

Trauma of the liver may be classified as direct and indirect. The former results chiefly from penetrating missiles, with the varying factors of size, velocity and direction. The magnitude of injury is primarily dependent upon the explosive effect of the missile, rather than its size. In these, the wound of entrance is much larger than that of exit. The lacerations are stellate and the tissue involvement is not confined to the area immediately surrounding the path of the projectile, but at a considerable distance, as seen in wounds of muscle. There is an associated vascular damage in the form of tears of large vessels, moderate to massive hemorrhage and severance of normal blood supply, producing further devitalization, necrosis and subsequent infection. The main hepatic vessels and bile ducts are rarely involved because of their protected position on the inferior surface. Following injury, there is usually profuse hemorrhage from the torn surface, along with drainage of bile from the interrupted ducts. In penetrating wounds of the lower thorax, the dome of the liver is most frequently involved, and the right more than the left. With such an associated wound of the diaphragm, extravasated blood and bile may find access to the pleural space and result in biliary empyema.

As opposed to direct trauma, nonpenetrating wounds have a lesser incidence, but may present identical pathologic findings, complications and outcome. Shedden and Johnson⁶ have classified this group according to the

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

WOUNDS OF THE LIVER

degrees of involvement and severity: (1) a rupture of liver tissue with simple laceration of Glisson's capsule represents minimal trauma; (2) separation of the capsule by subcapsular hemorrhage and damage to underlying structures occasionally occurs; (3) a central rupture with hemorrhage into the parenchyma can develop with possible later abscess formation. This classification does not take into account the size and depth of the wound, or degree of involvement of total tissue—factors which are of much value in prognosis.

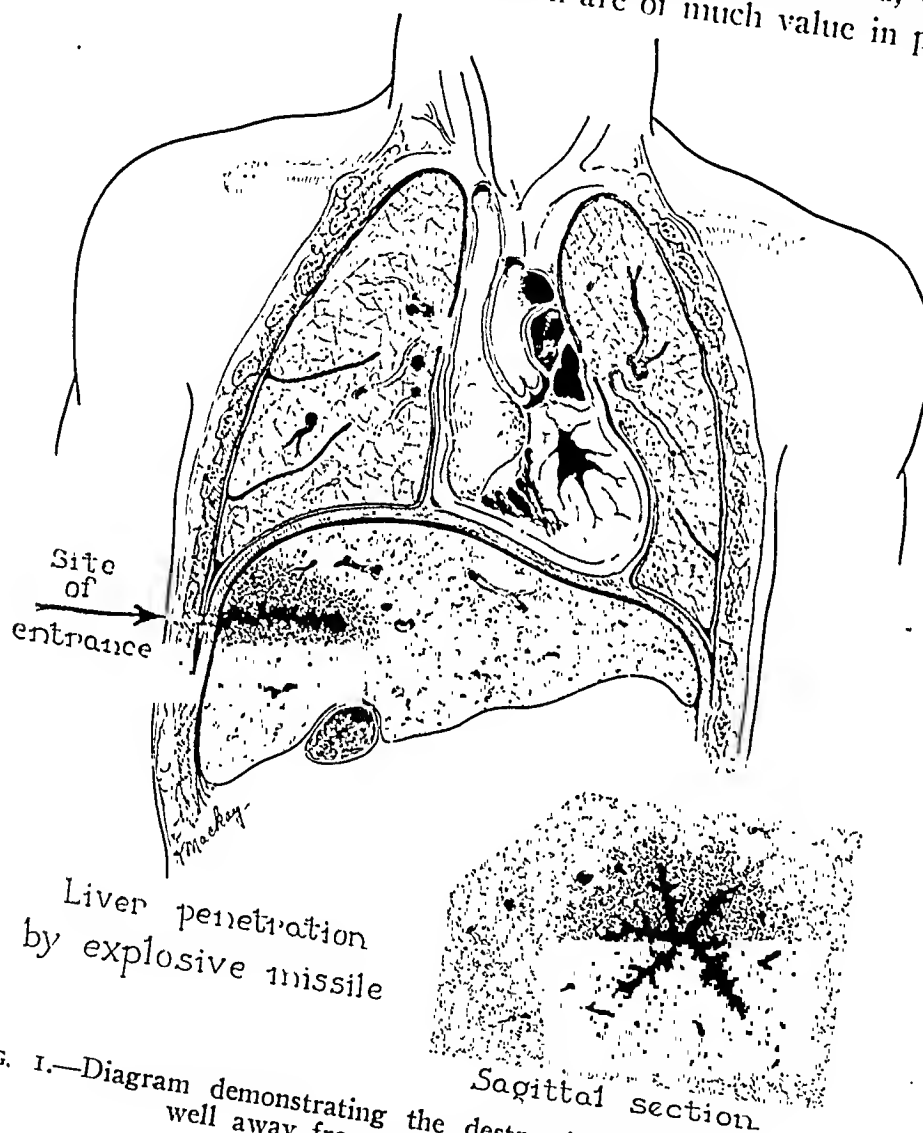


FIG. 1.—Diagram demonstrating the destruction of liver tissue well away from the missile tract.

In both direct and indirect trauma the pathologic findings are similar. Following cessation of hemorrhage from opened vascular channels, there remains a drainage from the biliary system, proportional to the amount of injury. Repair must be effected, first by a removal of devitalized and necrotic tissue, and later by regeneration of the structures destroyed. During tissue autolysis, vascular and biliary tracts may be further opened, and secondary hemorrhage and extravasation of bile occur.

Liver wounds may produce marked systemic manifestations, often out of proportion to the degree of injury. During the period immediately following injury, shock may be profound and not always equivalent to blood loss.

Following recovery from this initial period, secondary manifestations appear. These are concerned mainly with blood loss, biliary extravasation, hepatocellular damage, and occasionally associated renal dysfunction. The signs and symptoms of acute anemia may be seen, along with those of intraperitoneal hemorrhage. Bile peritonitis and empyema may now become manifest. Hepatocellular damage is demonstrated in a number of ways, each relating to a particular function performed by liver cells. The presence of jaundice is usually manifested late, of slight degree and transient. Interference with the deaminization of amino acids and the proper utilization of glycogen may be shown by lowered blood protein and an abnormal carbohydrate tolerance. Fibrinogen formation may be deficient and prothrombin may drop to a critically low level and thereby increase the clotting time of the blood.

The most serious complication of liver trauma is the occurrence of the so-called hepatorenal syndrome, which more often follows extensive crushing trauma than penetrating wounds. Hyperpyrexia develops, the pulse becomes weak and rapid, extreme restlessness is manifest, and often delirium and collapse supervene, followed in some cases by death. Oliguria is first seen with red blood cells, casts and albumin in varying amounts, and may be succeeded by anuria. Nonprotein nitrogen and creatinine progressively increase in blood concentration. Blood sugar, cholesterol and plasma chlorides are usually unaltered. In the presence of anuria, retention of fixed acids occurs, leading to a depletion of alkali reserve and a lowered carbon dioxide combining power.

The nature of the hepatorenal syndrome has not been satisfactorily determined. In many ways it is analogous to the "crush syndrome" seen following trauma to extremities. Orr and Helwig^{7, 8} thought it to be due to the effect on the kidney of a soluble toxin produced by necrosis of the liver. Boyce⁹ is of the opinion that a toxin may be produced in necrotic liver tissue, but that the renal damage is due to "an increase of its normal detoxifying duties, which are increased by failure of the detoxifying function of the liver rather than by any specific action of the toxin." Coller⁷ suggested a possible explanation on the basis of alterations of physiologic processes such as are produced by shock, hypotension, dehydration, alkalosis, and hyoproteinemia. Massive damage is a prerequisite for the appearance of this complication. Boyce and McFetridge⁹ have experimentally produced this condition in dogs by heterogenous liver implants in the peritoneal cavity. These results, and others,¹⁰ point to the emphasis to be placed on attempting to remove all damaged liver tissue which is definitely necrotic and may precipitate such a reaction.

EXPERIMENTAL CONSIDERATIONS

Clinically, it is desirable to ascertain whenever possible the degree of functional impairment of the liver following injury. This affords some index as to indicated treatment and prognosis. To demonstrate any correlation that might exist between the proven extent of liver damage and the results of easily applied clinical tests, the following experiments were undertaken:

WOUNDS OF THE LIVER

FIG. 2

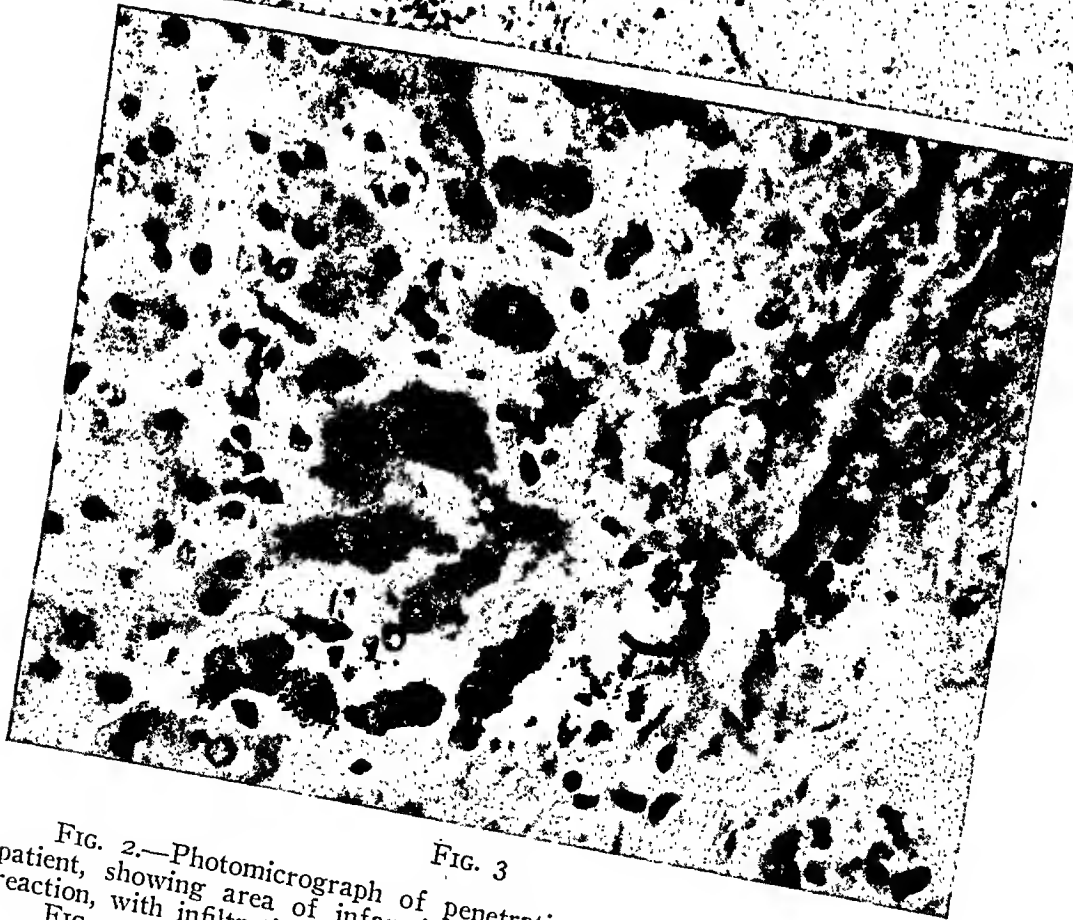
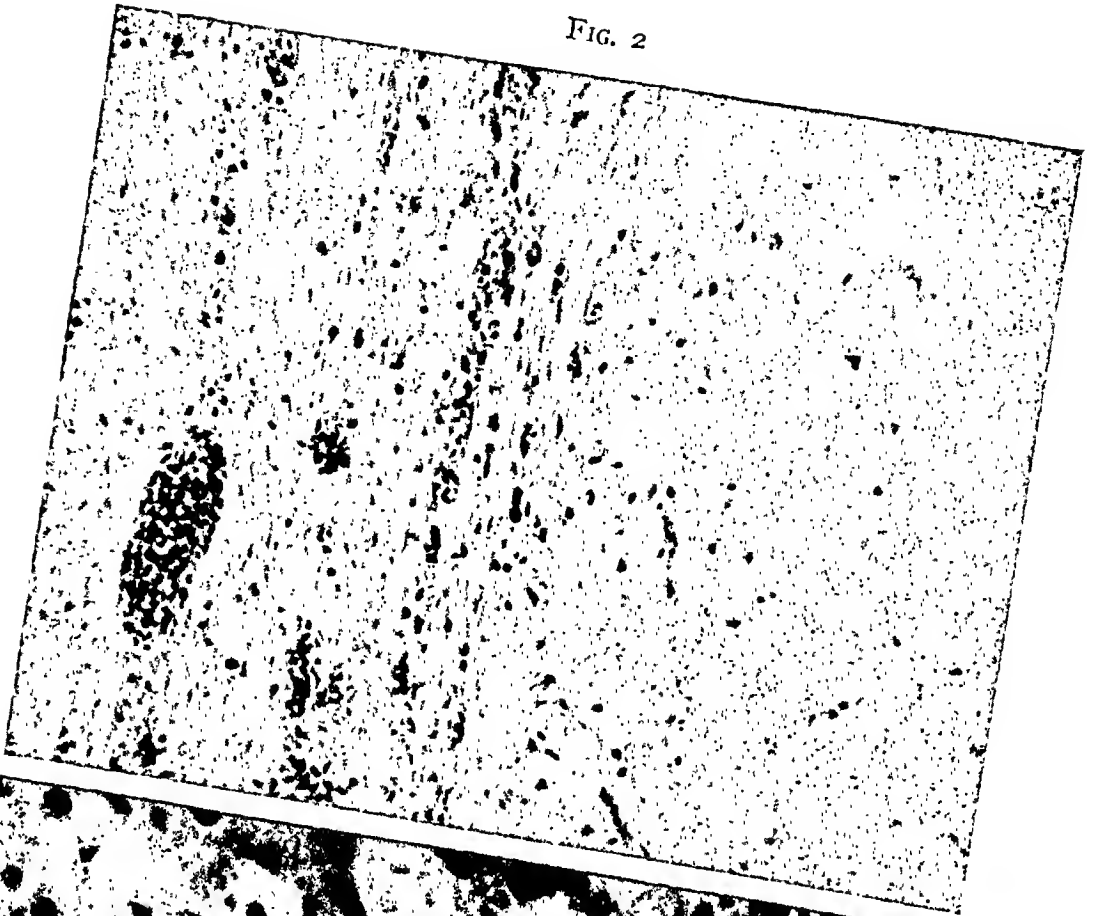


FIG. 3

FIG. 2.—Photomicrograph of penetrating wound of the liver of a patient, showing area of infarction and the surrounding inflammatory reaction, with infiltration of leukocytes and fibrosis.

FIG. 3.—Photomicrograph of liver of patient showing disruption of the liver cords with fibroplasia away from the site of injury.

A group of dogs, weighing 10 to 20 kilograms each, was selected. Control determinations were made on the intact animals, for galactose tolerance, brom-sulfathalein excretion, alkaline phosphatase activity in serum and prothrombin time. In the case of the first two, the intravenous methods were employed. All tests are those described in standard texts.

The dogs were given intravenous pentobarbital sodium in dosages of 64 milligrams for each five pounds body weight. Control determinations were

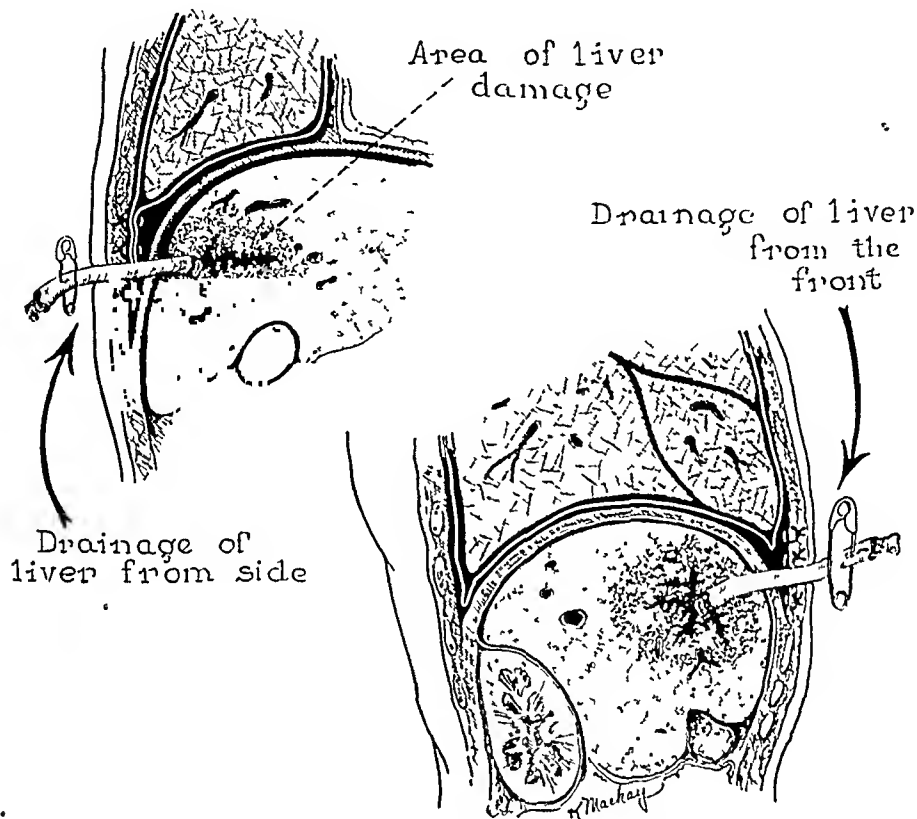


FIG. 4.—Drawing representing the method of drainage when the wound is high and lateral. The diaphragm has been fixed to the chest wall, closing-off the pleural cavity. A direct approach may be made to the area of damage, near the dome of the liver. The location of the drain is shown when the damage is anterior and superior.

again performed, and no appreciable differences were noted between intact unanesthetized animals and those under anesthesia.

Dogs were then selected in pairs, anesthesia induced, celiotomy performed, and the liver exposed. Varying amounts of liver were subjected to manual trauma, rapidly striking the individual lobes approximately fifty times. This produced evidence of considerable damage, as shown by minor tears in Glisson's capsule, subcapsular hemorrhage, external hemorrhage. In some animals it was estimated that 50 per cent of the liver tissue had been damaged, and in others this percentage was higher, all the lobes having been traumatized. The abdomens were then closed. All the animals survived this procedure. In some there was a moderate degree of postoperative shock, which

was treated with intravenous infusions of physiologic saline, with good response.

One hour after trauma, the various clinical determinations were again made, blood samples being drawn at intervals of 30 minutes for one and one-half hours. The results, as well as the control curves, are shown in the accompanying diagrams.

At the end of six days some of the animals were again given an anesthetic and samples of blood drawn for the determinations. The abdomens were then opened and the livers examined, specimens were taken for histopathologic study. Grossly, the surface of the liver in most instances had become covered by omentum, particularly in those which had superficial capsular tears on the anterior and inferior surfaces. Areas of infarction and yellow necrosis were evident.

It was remarkable that following the initial period of shock and recovery from the anesthetic, the animals showed little evidence of being ill, ate heartily, were alert and would exercise when given the opportunity.

The conclusions that may be drawn from this preliminary report of the work in progress center chiefly about the obvious fact that the liver has a very large functional reserve, as well as tremendous recuperative and regenerative powers.

TREATMENT

In rupture of solid viscera, particularly the liver and spleen, treatment revolves about control of hemorrhage. This can be easily effected in the spleen by its removal. The liver, however, is such a friable organ that it can be seldom sutured. Approximation of the edges by sutures which are tight enough to prevent hemorrhage from the damaged surfaces will result in cutting of the tissues. However, with minimal wounds near the periphery, sutures may occasionally be used advantageously. Whenever damaged tissues are placed in apposition, the processes of repair are delayed, necrosis and sloughing must occur before union is complete.

Hemorrhage is controlled in most instances by packing. The possibility of infection is increased by this procedure and after removal, secondary hemorrhage may occur and necessitate repacking. A liver which has been too tightly packed may develop pressure necrosis. When wounds are extensive and located in inaccessible positions, particularly beneath the diaphragm, the control of hemorrhage becomes difficult. As a rule, packing is brought out through a separate stab wound; it is sometimes necessary to re-enter this wound and compress the area from which hemorrhage occurs.

Recently, several new materials have shown promise as hemostatic agents.^{11, 12} Among these are oxidized cellulose, fibrin and gelatin foam. An ideal material should control bleeding, act as a drain, and undergo absorption within a safe period as regeneration of liver tissue takes place.

Muscle grafts, in many instances, are beneficial, but with extensive damage it is not always feasible to place a sufficiently large section of muscle over the area of hemorrhage. The chief disadvantage of muscle graft is its inability to

FIG. 5

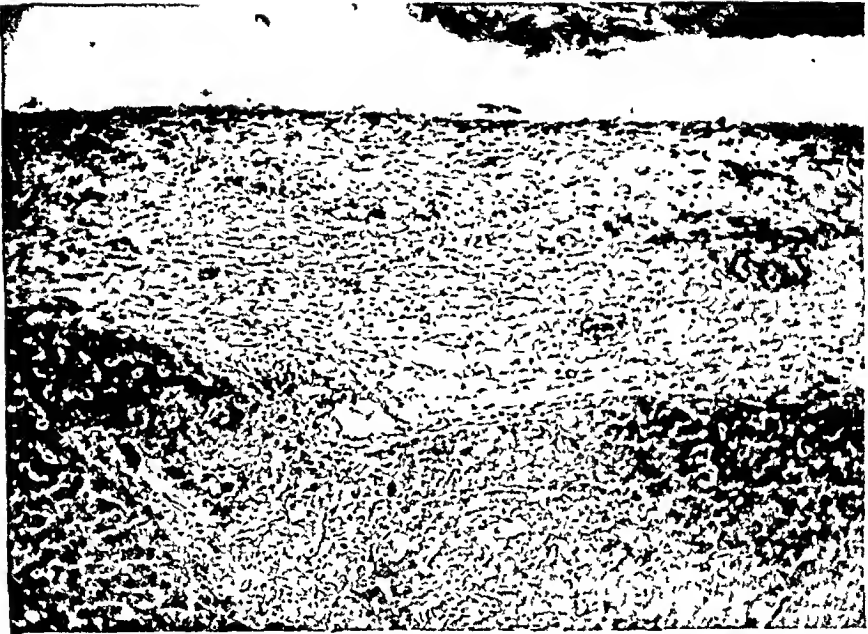


FIG. 6

FIG. 5.—Photomicrograph demonstrating healing process and the formation of fibrous tissue after a laceration of the liver in the dog, without traumatizing the underlying structures.

FIG. 6.—Photomicrograph demonstrating healing of a liver in which gelatin foam has been placed into preformed tract into the substance of the liver. The formation of fibrous tissue and the development of new blood vessels and infiltration with leukocytes are demonstrated in the trabeculae of the gelatin foam.

become fixed and remain so for any length of time. On damaged liver it will not adhere and healing does not occur until the necrotic tissue is removed.

Fibrin foam can be successfully used for the control of hemorrhage from the liver surface. It is most effective in wounds in which there is mild oozing

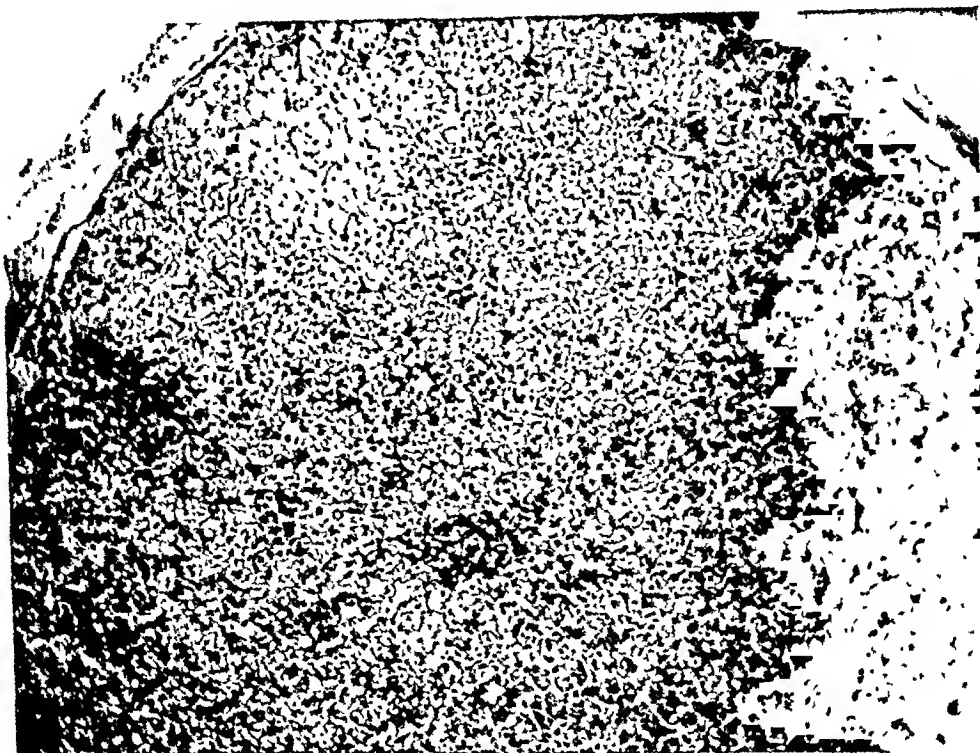


FIG. 7-A.—Photomicrograph of the liver of a dog traumatized two weeks before. There is marked evidence of necrosis, fatty degeneration and leukocytic infiltration. The greatest evidence of necrosis occurs near the surface at the site of the trauma.

DOG #1	RETENTION EXCRETION AFTER 30 MINUTES	ALKALINE PHOSPHATASE	GALACTOSE TOLERANCE 30, 60, 90, MINUTES AFTER INJECTION	PROTHROMBIN TIME
TRAUMA	PER CENT	UNITS	MG %	SECONDS
BEFORE	10%	6.7	124 - 69 - 0	18
AFTER 1 HR.	25%	12.9	94 - 31 - 0	21
24 HRS.	20%	10.3	38 - 18 - 0	19
1 MO	15%	9.1	34 - 15 - 9	20

FIG. 7-B.—Chart representing functions before trauma to the liver of a dog (as shown in Fig. 7-A) and the results at various intervals afterwards. It is noted that there is no appreciable reduction in these functions following trauma.

from a cut-surface. Its use in this respect represents the ideal type of pack when placed on a surface with a minimum of damaged tissue, and close adherence is obtained. Unfortunately, the majority of wounds of the liver do not present this type of bleeding.

Jenkins¹¹ has shown that gel foam (bovine thrombin incorporated in a gelatin matrix), used on a cut-liver surface, accomplishes excellent hemostasis. Absorption is effected in the presence of leukocytes. This substance is



FIG. 8-A.—Photomicrograph of a liver of a dog which was traumatized three weeks before sections were made. There is still evidence of marked destruction well away from the site of the trauma in the substance of the liver, with moderate fatty infiltration and leukocytic infiltration.

DOG # 4				
TRAUMA	RETENTION EXCRETION AFTER 30 MINUTES PER CENT	ALKALINE PHOSPHATASE UNITS	GALACTOSE TOLERANCE 30, 60, 90, MINUTES AFTER INJECTION MG %	PROTHROMBIN TIME SECONDS
BEFORE	3 %	13.9	50-26-0	22
AFTER 1 HR.	15 %	12.4	31-6-0	20
1 MO.	8 %	11.2	31-20-9	22

FIG. 8-B.—Chart representing results of functional tests of liver of dog (Fig. 8-A) before and after direct trauma to the liver. It is noted, as in previous dogs, that no appreciable change is denoted after the liver had been directly traumatized.

promising, but as yet there is no ideal material for the control of hemorrhage from the traumatized liver.

In the repair of liver wounds it is essential to close carefully all openings in the diaphragm. This has a dual purpose: (a) to restore the integrity of the abdominal and thoracic cavities and prevent the passage of bile and blood

into the pleural sac, where it is tolerated less than in the peritoneal cavity, (b) to restore the mechanics of the respiratory system and prevent the formation of a diaphragmatic hernia.

Inasmuch as the extent of cellular damage is greatly beyond the actual tract of the projectile, the ideal procedure would be primary débridement of the nonviable tissue. It is difficult to estimate the extent of damage at the time of operation. However, if this could be determined and the devitalized tissues removed, healing could then occur without sloughing and infection. A disadvantage of débridement is the hemorrhage which accompanies it. With the advent of a better substance for controlling hemorrhage, primary débridement could then be performed in the same manner as it is now done in other tissues.

At the present time, drainage of liver wounds must always be carried out to control bleeding and to allow escape of bile, blood and the products of infection and tissue necrosis. As mentioned before, drains should be brought out through a separate stab incision, most advantageously placed beneath the costal margin. Drainage by way of the transthoracic route is obviously not tenable. Drains should not be placed in the celiotomy incision because this favors herniation of the omentum and increases the likelihood of wound dehiscence. The wound of entrance or exit may at times be employed for drainage, provided there is no communication with the pleural space and dependency is assured. With lateral wounds of the diaphragm, following firm closure by suturing of this muscle to the anterolateral thoracic wall, drains may be placed directly to the site of the wound. The wound in the chest wall is excised, and the overlying ribs are removed to allow a direct approach to the liver.

The period of drainage cannot be arbitrarily set. If drains are satisfactorily placed and the control of hemorrhage is accomplished during the first hours or days, the tendency is to remove the drain too early. If it functions as both a drain and a pack there will be a minimal bleeding and drainage of bile. The drains may become adherent and cause secondary hemorrhage upon removal. Gradual removal over a period of days is more satisfactory. When the wound is of sufficient size and the peritoneal cavity well-sealed, it may be necessary to reinsert a drain to allow continued escape of bile. During the process of subsequent healing a large amount of tissue slough and bile drainage will take place. Healing will not occur until full sequestration of the destroyed tissue takes place and fibrosis occurs. If the wound is allowed to close or is blocked by too large a drain, bile accumulates, infection follows, and may lead to the formation of an abscess within, above or below the liver.

The general care of wounds of the liver are of paramount importance throughout the course following injury. During the first phase attention is directed towards fluid replacement and correction of the hemorrhage and shock. Surgery should not be undertaken until full response has been made, but there occasionally exists protracted failure to respond to blood replacement and immediate operation to control the continued bleeding is necessary

in spite of the existent shock. The general postoperative care must be instituted in addition to maintenance of fluid balance, protein equilibrium and a correction of vitamin deficiencies. The factors which govern systemic therapy are mainly the degree and the type of injury and the complications.

SUMMARY

1. Wounds of the liver constitute one of the major problems of abdominal injuries.

2. The manifestations depend on the indirect and direct forms of trauma.

3. The pathologic effects are similar in each and are proportional to the degree of initial trauma and subsequent complications.

4. Clinical manifestations are presented in the form of hemorrhage, shock, renal insufficiency and infections.

5. Following trauma, the liver has a remarkable recuperative power.

6. If large amounts of tissue are devitalized, repair will be delayed until full sequestration occurs. This process further increases the likelihood of hemorrhage and escape of bile.

7. There is evidence to suggest that in the dog, the usual functional tests are not greatly affected following massive trauma to the liver.

8. The complications are for the most part proportional to the degree of involvement, subsequent interference with blood supply and associated infection.

9. It is felt that when materials for control of hemorrhage are perfected, primary débridement of the damaged liver should be performed, as in wounds of soft tissues.

REFERENCES

- ¹ Fox, D. B.: Thoraco-abdominal Wounds. *S. G. & O.*, 82, 64-70, 1946.
- ² Madding, G. F., Lawrence, K. B., and Kennedy, P. A.: War Wounds of the Liver. *Bull. U. S. Army Med. Dept.*, 5, 579, 1946.
- ³ Mann, Frank C.: Effects of Complete and Partial Removal of Liver. *Medicine*, 6, 419, 1927.
- ⁴ Mann, Frank C.: Hepatic Function in Relation to Hepatic Pathology. *Ann. Int. Medicine*, 8, 432, October, 1934.
- ⁵ Irenus, Carl, and Puestow, Chas. B.: Effect of Massive Experimental Hemorrhage on Hepatic Function in Dogs. *Arch. Surgery*, 49, No. 2, 100, August, 1944.
- ⁶ Shedden, W. M., and Johnston, F.: Traumatic Rupture of the Liver. *New Eng. J. Med.*, 213, 960-965, November, 1935.
- ⁷ Orr, T. G., and Helwig, F. C.: Liver Trauma and Hepatorenal Syndrome. *Am. Surg.*, 110, 682-692, October, 1939.
- ⁸ Helwig, F. C., and Schutz, C. B.: Liver Kidney Syndrome: Clinical, Pathological and Experimental Studies. *S. G. & O.*, 55, 570, November, 1932.
- ⁹ Boyce, E. F., McFetridge: Autolysis of Tissue in Vivo. *Arch. Surg.*, 34, 977-996, June, 1937.
- ¹⁰ Ellis, J. C., and Dragstedt, R. R.: Liver Autolysis in Vivo. *Arch. Surg.*, 20, 8-16, January, 1930.
- ¹¹ Jenkins, Hilger, P., Janda, Rudolf, and Clark, James: Clinical and Experimental Observations on Use of Gelatin Sponge or Foam. *Surgery*, 20, 124-132, July, 1946.
- ¹² Frantz, V., and Lattes, R.: Oxidized Cellulose: Absorbable Gauze. *J. A. M. A.*, 129, 798, November, 1945.

DISCUSSION.—DR. T. C. DAVISON, Atlanta, Ga.: I just want to stress one point. I have observed not only in civilian practice but in an Evacuation Hospital, in France, in 1918, that any penetrating wound of the chest below the nipple line, particularly on the right side, is apt to injure the liver. We reached the point where we always explored the abdomen in such cases, particularly if there was no site of exit, because nobody knew where that missile had gone. Roentgenograms would locate the foreign body but did not show what organs had been damaged—the dome of the liver, the stomach, the kidneys, the spleen, the intestines, and sometimes the spinal cord. I just want to say that in such wounds exploration is advisable.

DR. MICHAEL E. DEBAKEY, New Orleans, La.: Doctor Davison's mention of wounds of the liver in World War I prompts me to present some statistical data on similar wounds in World War II, based upon records and analyses made available to the Office of the Surgeon-General. Many of these data were recorded by the Second Auxiliary Surgical Group, which had an extensive experience in the Mediterranean Theater of Operations.

Abdominal injuries in World War II comprised approximately 6 per cent of all wounds, and wounds of the liver comprised about 25 per cent of all abdominal wounds. In World War I wounds of the liver comprised 13 per cent of all abdominal wounds, which is about half of the World War II incidence. Uncomplicated hepatic injuries, that is, liver injuries not associated with injuries to other viscera, constituted about 40 per cent of the total wounds of the liver in World War II, and complicated wounds constituted about 60 per cent. In World War I these respective percentages were 75 and 25. It will be observed from the comparative figures that there is a significantly higher total incidence of hepatic injuries in World War II, and an increase in the ratio of complicated to uncomplicated injuries. The conclusion seems justified that in World War II a larger proportion of severely wounded men were observed before death and were submitted to surgery.

Of particular interest from the standpoint of prognosis in World War II is the so-called multiplicity factor, which refers to the number of abdominal organs injured in a given case, as determined at operation. The case-fatality rate calculated on this basis increased in almost direct proportion to the number of viscera injured. For uncomplicated wounds of the liver the case-fatality rate was about 10 per cent; when one other viscus was injured, it was about 28 per cent; when two other organs were injured, it was almost 40 per cent; when three others were injured, it was almost 55 per cent; when four others were injured, it was about 85 per cent. According to the Second Auxiliary Surgical Group, which provided perhaps the best available statistics on the subject for World War II, the total mortality for wounds of the liver in that war was 27 per cent, which is a very distinct improvement over the World War I figure of 66 per cent.

As to treatment of wounds of the liver, experience proved that the best results were secured by the establishment of adequate external drainage of bile and the products of traumatized tissue. Early in the war dry packs were frequently used, but the results were not good and eventually this method was entirely discarded.

According to the statistics of the Second Auxiliary Surgical Group, shock was the cause of death in something over half of the fatal hepatic injuries. Pulmonary complications were responsible for the fatalities in about 17 per cent of the cases and peritonitis in about 12 per cent. Oliguria and renal failure were present in 8.5 per cent of the deaths, and the question was raised of the possible relationship of liver damage to renal failure; the so-called transfusion or shock kidney, however, could not always be excluded. The remaining proportion of fatalities was attributable to various miscellaneous causes, which were not always connected with the hepatic injury. The most frequent complication of hepatic wounds was subphrenic abscess, with biliary empyema and intrahepatic abscess next in order of frequency. Complications could often be traced to inadequate drainage.

WOUND DISRUPTION AND EARLY AMBULATION*.

JOHN C. BURCH, M.D., AND CLOYCE F. BRADLEY, M.D.

NASHVILLE, TENN.

EARLY AMBULATION is a valuable method in the management of postoperative patients. Based on sound physiologic principles, it not only reduces the incidence of vascular and pulmonary complications, but appreciably shortens convalescence. These clear-cut results have won it many advocates. Nevertheless, there is still a certain deep-rooted scepticism concerning the danger of wound disruption. This is the greatest deterrent to the general acceptance of the method. In the hope of clarifying this point, it is the purpose of this paper to present a study of the disruptions of abdominal wounds in patients treated at conventional bed rest and in those subjected to early rising.

The importance and frequency of wound disruption as a surgical complication have been extensively discussed in the surgical literature. Excellent reviews are at hand in the articles of Singleton and Blocker,¹ Glenn and Moore,² Fallis,³ and Jenkins,⁴ as well as a host of others. The incidence of disruption varies from 0 in 16,456 celiotomies by Baldwin⁵ to 1.8 per cent by Kraybill.⁶ The average is about 0.6 per cent. Upper abdominal operations are somewhat more prone to disruption than lower abdominal ones. Glenn and Moore² report 0.92 per cent for biliary tract operations, 1.55 per cent for stomach operations, and 1.96 per cent for large bowel operations. In gynecologic work, Schmitz and Beaton⁷ report 0.15 per cent, and Hesselstine and Bohlender⁸ 0.442 per cent. The mortality of disruption varies from 32 per cent to 68.7 per cent.

Three groups of cases have been selected for this study. In one group are included 856 abdominal cases operated upon at St. Thomas Hospital between January 1, 1946 and July 31, 1946. The great majority of these were treated in the conventional manner.

In the second group are 1908 celiotomies observed at the Brooke General Hospital. All were subjected to early ambulation, unless specifically contraindicated. These have been previously reported in part.⁹ Since the majority of patients in the Brooke series were healthy young soldiers, the two are not exactly comparable. However, there is some similarity, as included are a very sizable number of women, veterans, retired personnel and children. To provide more comparable data, a small series of 138 recent private cases are added. All were personally operated upon and followed.

In the St. Thomas series (Table I), there were 856 celiotomies with subsequent abdominal wound disruption in nine, or 1.05 per cent, of the incisions. Seven hundred and twenty-six, or 84.81 per cent, of the incisions were in the

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

WOUND DISRUPTION AND AMBULATION

TABLE I

LAPAROTOMIES AT ST. THOMAS HOSPITAL— JAN.1, 1946 TO JULY 31, 1946

TOTAL	DISRUPTIONS	%
856	9	1.05

ABDOMINAL INCISIONS

TYPE OF INCISION	NO.	%	DISRUPTIONS	%
LOWER ABDOMINAL	726	84.81	3	0.41
UPPER ABDOMINAL	129	15.19	6	4.65

UPPER ABDOMINAL INCISIONS

TYPE	NO.	%	DISRUPTIONS	%
VERTICAL	97	75.19	6	6.19
TRANSVERSE	32	24.81	0	0.00

TABLE II

SUTURE MATERIAL IN FASCIAL CLOSURE — UPPER ABDOMINAL

INCISION	SILK AND COTTON	CAT GUT INTERRUPTED	CAT GUT CONTINUOUS	TOTAL
VERTICAL	60	29	9	98
TRANSVERSE	29	1	1	31
TOTAL	89	30	10	129

SUTURE MATERIAL IN PERITONEAL CLOSURE — UPPER ABDOMINAL

INCISION	INTERRUPTED SILK OR COTTON	CONTINUOUS CAT GUT	CONT. CAT GUT REINFORCED
VERTICAL	0	66	31
TRANSVERSE	12	15	5
TOTAL	12	81	36

lower abdomen, with three, or 0.41 per cent, disruptions. One hundred and twenty-nine, or 15.19 per cent, of the incisions were in the upper abdomen, with six, or 4.65 per cent, disruptions. Ninety-seven, or 75 per cent, of all upper abdominal incisions were vertical in type. All six of the upper abdominal wound disruptions occurred in this group of vertical incisions, with a group incidence of 6.19 per cent. In the upper abdominal cases (Table II), the fascia was closed with interrupted silk or cotton in 89, with interrupted catgut in 30, and with continuous catgut in ten. The peritoneal closure was with interrupted silk or cotton in 12, continuous catgut in 81, and continuous catgut reinforced with silk or cotton in 36. In the upper abdominal disruptions (Table

TABLE III

CLOSURE IN UPPER ABDOMINAL DISRUPTIONS

	SILK AND COTTON	CAT GUT INTERRUPTED	CATGUT CONTINUOUS
FASCIA	4	2	0
	INTERRUPTED SILK AND COTTON	CATGUT CONTINUOUS REINFORCED	CAT GUT CONTINUOUS
PERITONEUM	0	1	5

UPPER ABDOMINAL DISRUPTIONS

PERITONEAL CLOSURE WITH CONTINUOUS CAT GUT		
81 CASES	5 DISRUPTIONS	6.1%
PERITONEAL CLOSURE WITH INTERRUPTED COTTON AND SILK OR CONTINUOUS CAT GUT REINFORCED WITH INTERRUPTED COTTON AND SILK		
48 CASES	1 DISRUPTION	2.08%

III), the fascia was closed with interrupted silk or cotton in four and interrupted catgut in two, the peritoneal closure in five instances was continuous catgut, and, in one, continuous catgut reinforced with interrupted silk. There were five, or 6.17 per cent, disruptions in the 81 upper abdominal cases in which the peritoneum was closed with continuous catgut and only one, or 2.08 per cent, in the group of 48, in which the peritoneum was closed entirely with interrupted cotton or silk, or in which the continuous catgut was reinforced with interrupted cotton or silk. The diagnoses in the cases disrupting, and the operations performed are shown in Table IV.

Five of the nine cases of disruption occurred following operations on the stomach, and four of the nine were in individuals suffering from malignant disease. In two instances, the disruptions were treated by strapping the wounds. In one, through-and-through sutures of silkworm gut were utilized, while in the other six, the closure was in layers. Three of these were reinforced by through-and-through sutures. Two patients died—a mortality of 22.2 per cent.

In the Brooke General Hospital series, there were 1,908 representative abdominal cases, excluding hernia. There was but one disruption following one

WOUND DISRUPTION AND AMBULATION

of the 83 operations on the biliary tree. In this case, the incision was a right-Singleton, the fascia was closed with interrupted cotton, and the peritoneum with continuous catgut reinforced with interrupted cotton. The disruption was precipitated by intractable hiccoughs. It did not extend throughout the wound, and was easily handled by strapping. This patient subsequently died as the result of coronary occlusion, bile peritonitis, and pneumonia.

In the Brooke cases, much attention was devoted to wound closure. Interrupted cotton was used for the fascia, and interrupted cotton alone, or reinforced with continuous catgut, was used for the peritoneum. Transverse incisions for upper abdominal wounds were favored by the majority of the

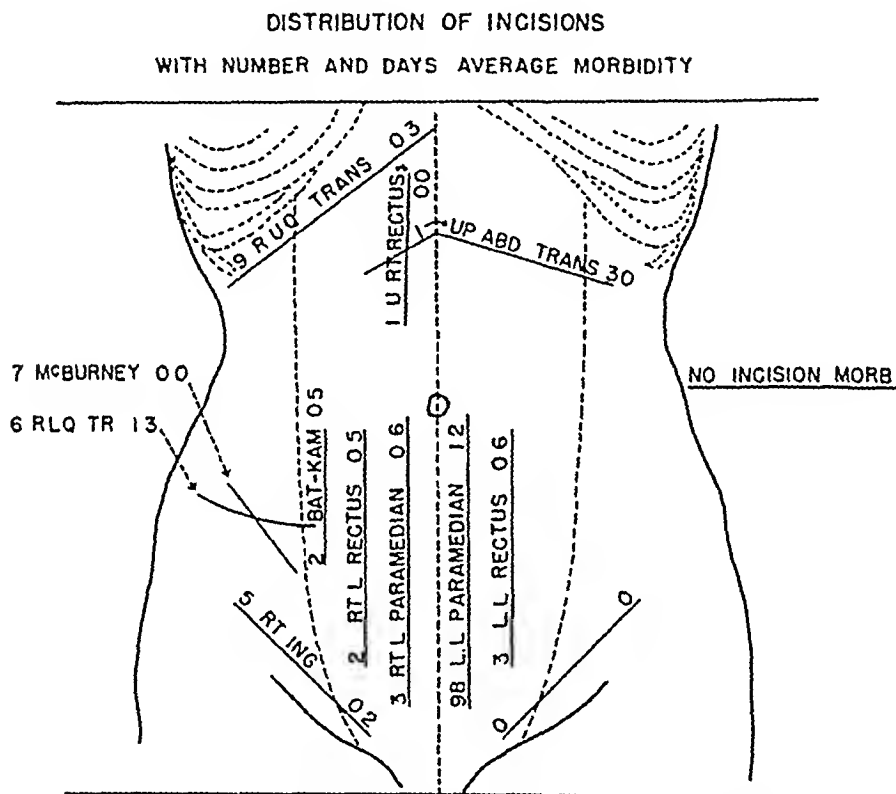


FIG. 1.—138 celiotomies subjected to early ambulation.

operators. However, many of the 90 operations on the stomach and duodenum were performed through vertical incisions. The McBurney incision, or a modification, was used routinely in the 932 appendicectomies. A left paramedian incision was the choice for pelvic operations.

In the 3rd group of 138 private patients, closure was with interrupted cotton through the peritoneum, fascia and skin. The locations of the incisions in the 3rd group of 138 private patients is shown in Figure 1. The figure at the end of the incision represents the number of days the temperature exceeded 100.4° F. Fifty-three per cent of the patients were ambulant on the first postoperative day (Table V), 31 per cent on the second, and 15 per

cent on the third. There were 13 pulmonary complications, no vascular complications, and two wound infections. There is one case listed as a disruption. Actually, there was no dissolution of the suture line, the eventration of the intestine occurring adjacent to a colostomy. In comparing the three groups of cases, it is clear that the incidence of wound disruption is far less in the early risers. This bears out the observation of many authors that wound healing is not impaired by early ambulation. The reports suggest it may be improved.

Ries¹⁰ says: "and I have yet to see the first hernia." Leithauser¹¹ had no dehiscence or postoperative hernia in 436 cases. In his later report, dehiscence, incisional hernia and recurrences following herniorrhaphy were not more frequent after early rising. There was no instance of eventration in his 900 cases. In 462 abdominal incisions Nelson¹² had three partial disruptions, two of which

TABLE IV

DISRUPTIONS AT ST THOMAS HOSPITAL JAN 1, 1946 TO JULY 31, 1946

UPPER ABDOMINAL	
DIAGNOSIS	OPERATION
GALL STONES	CHOLECYSTECTOMY
PERFORATED DUODENAL ULCER	CLOSURE
GASTRIC ULCER	GASTROENTEROSTOMY
DUODENAL ULCER	PARTIAL GASTRECTOMY
DUODENAL ULCER	GASTRO JEJUNOSTOMY
CARCINOMA STOMACH	GASTRO JEJUNOSTOMY

LOWER ABDOMINAL	
DIAGNOSIS	OPERATION
CARCINOMA SIGMOID	RESECTION OF SIGMOID
CARCINOMA BLAODER	URETERO-SIGMOIDOSTOMY
CARCINOMA RECTUM	ABDOMINO-PERINEAL RESECTION OF RECTUM

TABLE V

138 LAPAROTOMIES TREATED BY EARLY AMBULATION

% OF CASES AMBULANT		
1st DAY	2nd DAY	3rd DAY
53.6 %	31.2 %	15.2 %

COMPLICATIONS			
PULMONARY	VASCULAR	DISRUPTIONS	INFECTIONS
13	0	1	2

occurred in patients whose wounds had been closed with catgut, and for whom early ambulation had not been authorized. Powers¹³ allowed 39 herniae to rise early, and none recurred. In 39 controls treated by the traditional method of bed rest, there were two recurrences. Ashkins¹⁴ noted one bulging cholecystectomy wound and one weak scar, without protrusion, in 823 cases; Schafer and Dragstedt,¹⁵ in 102 cases, had one eventration and two postoperative herniae. Elman¹⁶ had no wound disruption in 79 cases, but noted three in his control group. Many others testify in the same vein. From an experimental point of view, Newburger¹⁷ produced standardized celiotomy wounds in rats and at intervals of 3-5-10 days, the strength of the wounds were determined in the animals which were kept at rest and in others which were exercised. Exercise, rather than immobilization, was found to hasten the increase in tissue strength of the experimental abdominal incision. The Russian, Kimbarovskiy¹⁸ studied wounds in dogs in the ambulant state, and dogs forced into the reclining position by means of plaster encasements. In the restricted animal, he concluded there was a decrease in fibroplasia.

The value of transverse or muscle-splitting incisions is clearly apparent. In a previous paper, Fisher and Burch⁶⁵ reported 1,500 appendicectomies through

a McBurney incision had no disruptions. Singleton and Blocker¹ report 470 transverse incisions in the upper abdomen, with no disruptions, and 292 verticals with nine disruptions. Rees and Coller²⁰ had 225 consecutive transverse incisions with no disruptions and only one hernia.

The technic of wound closure is of primary importance. The data clearly indicate that a continuous catgut closure of the peritoneum is followed by high rate of disruption. The importance of the peritoneum in maintaining the integrity of the abdominal wound is not sufficiently emphasized. The process of wound disruption does not proceed simultaneously throughout the wound.²¹ On the contrary, it is a progressive phenomenon, starting with a giving-way of the peritoneum and the gradual protrusion of the viscera through the layers of the wound. Freeman²² stresses the importance of the omentum acting as a wedge. When the skin stitches are removed, the slightest strain is enough to make the disruption complete. The fact that it was nearly complete at this time is shown by the appearance of the wound. Fresh bleeding is seen only in the skin. The deeper tissues do not bleed. They are edematous, matted together, and covered by glistening granulation tissue. It is usually obvious that the deeper separation is not recent.

The appearance of bloody drainage from an abdominal wound is suggestive of a dissolution of the peritoneal suture line.

To maintain the integrity of the peritoneum, Meleney and Howes²³ advocate a mattress type of suture in the posterior fascia and peritoneum over-sewn with a layer of fine catgut. The utilization of an interrupted suture in the peritoneum, combined with continuous catgut, has been effective in preventing peritoneal dissolution and subsequent disruption. The interrupted sutures must be placed fairly close together. We usually use three or four to the inch. If so placed, the continuous catgut may be safely eliminated. In a few cases, we have had an opportunity to open cases so closed, and the absence of adhesions along the peritoneal suture line was striking. While this valuable method is not in general use, its value has been recognized by Cave,²⁴ Hinton,²⁵ Meyer,²⁶ and others.

In conclusion, it may be said that early ambulation does not affect the abdominal wound adversely. The satisfactory wound healing, observed following early ambulation, may be attributable to a better nutritional state, as well as a lowered incidence of the many complications favoring disruption, such as vomiting, cough, distention, and urinary retention. It is a safe procedure of great benefit to the patient, and its possibilities in decreasing hospitalization are as yet unrealized.

BIBLIOGRAPHY

- ¹ Singleton, A. O., and Blocker, T. G.: The Problem of Disruption of Abdominal Wounds and Postoperative Hernia. *J. A. M. A.*, 112, 122-127, 1939. Quoted by Benjamin.¹
- ² Glenn, F., and Moore, S. W.: The Disruption of Abdominal Wounds. *Surg., Gynec. and Obst.*, 72, 1041-1046, June, 1941.
- ³ Fallis, L. S.: Postoperative Wound Separation: Review of Cases. *Surg.*, 1, 523-524, April, 1937.

- ⁴ Jenkins, H. P.: A Clinical Study of Catgut in Relation to Abdominal Wound Disruption: With a Test of its Tensile Strength on Patients. *Surg., Gynec. and Obst.*, 64, 648-662, March, 1938. Quoted by Bowen.²
- ⁵ Baldwin, J. F.: Disruption of Abdominal Wounds. *Am. J. Surg.*, 25, 7-11, July, 1934. Quoted by Bowen.²
- ⁶ Kraybill, W. G.: Total Disruption of Surgical Wounds of the Abdominal Wall: With Reference to Plasma Proteinemia and Plasma Ascorbic Acid. *Am. J. Surg.*, 66, 220-223, November, 1944.
- ⁷ Schmitz, H. E., and Beaton, J. H.: Wound Disruption and Its Management. *Am. J. Obst. and Gynec.*, 43, 806-814, May, 1942.
- ⁸ Hesseltine, H. C., and Bohlender, G. P.: Closure and Subsequent Care of Obstetric and Gynecologic Wound Disruptions. *Surg.*, 9, 40-50, January, 1941.
- ⁹ Burch, J. C., and Fisher, H. C.: Early Ambulation in Abdominal Surgery. *ANNALS OF SURGERY*, 124, 791-798, October, 1946.
- ¹⁰ Ries, E.: Some Radical Changes in After-Treatment of Coleotomy Cases. *J. A. M. A.*, 33, 454-456, August 19, 1899.
- ¹¹ Leithauser, D. J., and Bergo, H. L.: Early Rising and Ambulatory Activity after Operation: Means of Preventing Pulmonary and Circulatory Complications and of Shortening the Period of Convalescence. *Arch. Surg.*, 47, 203-215, August, 1943.
- ¹² Nelson, H.: Early Ambulation Following Section of the Anterior Abdominal Wall: Analysis of 426 Personally Conducted Cases. *Arch. Surg.*, 49, 1-8, July, 1944.
- ¹³ Powers, J. H.: The Abuse of Rest as a Therapeutic Measure in Surgery; Early Postoperative Activity and Rehabilitation. *J. A. M. A.*, 125, 1079-1083, August 19, 1944.
- ¹⁴ Ashkins, J.: Early Rising after Surgical Operations. *New England J. Med.*, 233, 33-37, July 12, 1945.
- ¹⁵ Schafer, P. W., and Dragstedt, L. R.: Early Rising Following Major Operations. *Surg., Gynec. and Obst.*, 81, 93-97, July, 1945.
- ¹⁶ Elman, R., and Akin, John T.: A Design for Surgical Convalescence. *ANNALS OF SURGERY*, 122, 716-733, October, 1945.
- ¹⁷ Newburger, B.: Early Postoperative Walking: The Influence of Exercise on Wound Healing in Rats. *Surg.*, 13, 692-695, May, 1943.
- ¹⁸ Kimbarovskiy, M. A.: Experimental Study on the Effect of Early Rising on Healing of Postoperative Wounds. *Navy khir. arkhiv.* 48, 116-121, 1940.
- ¹⁹ Fisher, H. C., and Burch, J. C.: The Treatment of Acute Appendicitis. *Southern Med. Journal*, 38, 235, April, 1945.
- ²⁰ Rees, V. L., and Collier, F. A.: Anatomic and Clinical Study of the Transverse Abdominal Incision. *Arch. Surg.*, 47, 136-146, August, 1943.
- ²¹ White, William Crawford: Disruption of Abdominal Wounds. *ANNALS OF SURGERY*, 99, 34-38, January, 1934.
- ²² Freeman, L.: The Cause of Postoperative Rupture of Abdominal Incisions. *Arch. Surg.*, 14, 600-604, February, 1927. Quoted by Bowen.²
- ²³ Meleney, F. L., and Howes, E. L.: The Disruption of Adominal Wounds, with the Protrusion of Viscera. *ANNALS OF SURGERY*, 99, 5-13, January, 1934. Quoted by Bowen.²
- ²⁴ Cave, H. W.: Incidence and Prevention of Incisional Hernias. *J. A. M. A.*, 101, 2,038-2,042, 1933. Quoted by Benjamin.¹
- ²⁵ Hinton, J. W.: Personal communication.
- ²⁶ Meyer, Carl: Personal communication.

DISCUSSION.—DR. ALFRED P. JONES, Roanoke, Va.: I wish to record the use of what might be called a continuous interrupted suture for the closure of muscle and fascia in abdominal wounds. A large full-curved needle is tied to each end of a long strand of the desired suture material. The first stitch is taken transversely through fascia only at the

lower end of the incision and tied so as to leave the suture of equal length on each side of the knot. With one of the needles, a bite is then taken through fascia and muscle on the left and brought up to catch fascia only on the right. With the needle attached to the opposite end of the suture, a corresponding bite is taken through muscle and fascia on the right, coming through to catch fascia above on the left. A square knot is then tied. This brings muscle-to-muscle and accurately approximates fascial edges.

The procedure is repeated for the length of the incision. Each interrupted stitch is independent, with the added security of having no loose ends to become untied, except for the terminal knot at the upper end of the incision.

DR. R. ARNOLD GRISWOLD, Louisville, Ky.: Several years ago, I had the opportunity of having an herniorrhaphy on myself, which taught me something about the tension on abdominal wounds. Any of you who have had an abdominal operation realize the tension on the wound when coughing, sneezing, or on a bedpan. If you get up early, as I did, you will realize the tension is much less, sitting or standing, than trying to use a urinal or bedpan in bed. We have run a small series of cases, putting a balloon attached to a water manometer into the abdomen following clean abdominal operations. The intra-abdominal pressure with the patient lying still in bed is about 20 cm. of water. The movements incident to arising from bed, walking across the floor and sitting down in a chair, cause a change in pressure to no more than about 20 cm. of water. However, when the patient in bed strains on a bedpan, coughs, or sneezes, pressure rises to 80 cm. or above.

DR. ROY D. McCLURE, Detroit, Mich.: I want to support Doctor Burch's paper, because for a number of years we have been using this method, early ambulation, with great satisfaction to us and to our patients. Having worked with Dr. Eugene Pool, in New York, from 1909 to 1912, opportunity was afforded to observe his patients who were given passive and active exercises in bed. There is no doubt that patients profited from this system, which was described in the J. A. M. A., 60, 1202, 1913.

In 1938, I read a paper on femoral hernia before this association (ANNALS OF SURGERY, 109, 987, 1939). I reported an operation on a very prominent man who had a strangulated femoral hernia; he refused to stay in bed, and had no complication. We have all had experience with babies and children who will not be quiet and who fight restraint. Their wounds heal solidly and hernia does not occur. We do not urge our patients to get out of bed; we give them the opportunity to do so and assume that they would rather go to the bathroom than use the bedpan. We prefer the transverse or oblique incisions, especially in gallbladder cases. We have a great many industrial hernia cases, and all are allowed bathroom privileges during the entire postoperative period.

DR. JOSEPH E. J. KING, New York, N. Y.: About 17 years ago, during a short visit to Nashville, I called on Dr. W. D. Haggard to pay my respects. He almost pulled me into his office and said he had something to tell me. He spoke of a celiotomy, which I believe was an hysterectomy, that he had performed several weeks earlier. He went in to see the patient on the second day postoperative and found her, in general, to be all right. He then looked at the dressing and noticed that there was a slightly yellow, wet spot about her buttocks about as big as "the bottom of a washtub." He stooped over and smelled it, thinking it might be urine, but there was no odor. He then took off the dressing and to his utter amazement found it to be "wringing wet." It was so wet he could squeeze fluid out of it. He inspected the line of incision and it appeared to be in perfect condition.

The next day the patient was not quite so well, but she was not sick. There was no more fluid on the sheet. The following day, *i.e.*, the 4th day postoperative, the patient was not doing well at all. Her temperature had risen to about 103° F. Doctor Haggard could not explain the wet spot on the sheet, nor the patient's condition. He took her to the operating room and removed the skin sutures. He found the wound beneath the skin completely separated with a knuckle of small intestine protruding through the musculature

and lying in a subcutaneous position. He freed the knuckle of intestine and resutured the incision. On the following day her temperature went to 105° F. and she died.

He went on to say that not more than three weeks later he had identically the same situation, but this time he knew what to do. He took the patient to the operating room immediately on the 2nd day, removed the skin sutures and found the same condition. He resutured the wound, and the patient made an uneventful recovery. He stated that he had never seen anything like these two cases before in his life, nor had he heard or read about such a condition.

It is well that he told me about these cases, for two or three months later I had a patient that presented the same picture. I informed the family physician about what should be done and told him what Doctor Haggard had told me. The family physician said: "The family would go crazy if you took that patient back to the operating room when he is no sicker than he is." I replied: "If we don't, the patient is going to die, because Doctor Haggard said so." He said he would assume the responsibility for the patient's condition. On the 4th day the patient was not doing well at all, his temperature had risen to about 103° F., and he did not look well. The family physician then said: "We must go ahead and see." I told him it was too late, but we took him to the operating room, opened the skin incision and found exactly what Doctor Haggard had described. The wound was resutured readily and the patient was returned to his room, but he died on the 5th day, with a temperature of 105° F.

About three months later the same family physician and I operated upon a patient whose story was identical with those described above. As soon as the doctor saw the wet spot on the bed he said: "Let's go!" We took the patient to the operating room, removed the skin sutures and found the same situation as described. The incision was resutured, and the patient made an uneventful recovery.

I have never seen another case like these two, and they were exactly as Doctor Haggard described his cases to me. I have related the story a number of times to colleagues from all over the country, and I have received 25 or 30 letters from some who have had the same experience. They told of meeting with the same resistance from the family physician but, instead of waiting, they resutured the wound immediately when the condition had been observed—always on the 2nd day—without loss of any of the patients.

In conclusion, should any of you ever see a large wet spot about the patient's buttocks on the 2nd postoperative day, and it does not smell like urine, I strongly advise that you immediately explore the incision.

DR. THOMAS O. OTTO, Miami Beach, Fla.: Doctor Burch has presented an excellent paper. In wound closure the choice of suture material is of great importance, and early ambulation is of great benefit in the improvement of circulation and avoidance of postoperative complications. Since my return from the Service it has been my misfortune to encounter three cases of wound disruption.

One case, an infant seven days old with congenital hypertrophic stenosis, demanded prompt surgical intervention. Two cases in the seventh decades of life suffered gastric carcinoma, obstructing totally. All three cases were extremely malnourished and prompt surgery was indicated. The infant was closed with silk and the adults were closed with cotton. Immediate steps to correct avitaminosis and hypoproteinemia were instituted. All three cases showed serum protein levels of four, or less, at the time of surgery. Secondary closures with through-and-through silver wire sutures were carried out in all three cases. The infant and one adult survived and one adult succumbed. Wound healing was perfect in the two survivors after blood serum protein levels were built up to 6.5, or higher. Correction of the hypoproteinemia is of greater importance than the choice of suture material.

In cases of malnutrition and low serum protein levels the employment of through-and-through silver wire sutures as a prophylactic against disruption suggests itself, until avitaminosis and serum protein levels can be restored to normal.

DR. FRANK K. BOLAND, Atlanta, Ga.: This discussion reminds me of a case I had forgotten about. I am like the man who said there were three things he could not remember: one was people's names; one was people's faces; and the third—well, he had forgotten what the third thing was.

This is the case of a large lady upon whom I performed a cholecystectomy. I took the stitches out about the 8th day. I had to leave town that night and got back the next morning, and I generally look at the wound the day after the stitches are removed. Lo and behold! she was sewed up. I said: "I thought I took these stitches out yesterday; there must be some mistake about it." So I proceeded to remove them again. Then I found that she had disrupted during the night and Doctor Ferguson had gone in and sewed her up again, and the nurse had failed to notify me of the event. Doctor Ferguson's repair of the wound held good, although the sutures had been in place less than 18 hours.

DR. JOHN C. BURCH, Nashville, Tenn.: (closing): I want to thank you for the discussion. Early ambulation is but one phase of what may be called mobilization of the patient. In those who cannot immediately get out of bed, voluntary exercises are important. Early exercise will help in the prevention of thrombophlebitis and pulmonary embolus. These exercises must be started on the first postoperative day. In my opinion, retention sutures are of no value, and I have long since abandoned them. The through-and-through closure is a makeshift method and is followed by a high percentage of herniae and evisceration. Much progress can be made by greater utilization of the transverse incisions and the abandonment of continuous sutures of absorbable material.

WOUND CLOSURE WITHOUT THE USE OF GRAFTS*

THOMAS O. OTTO, M.D.

MIAMI, FLORIDA

SURGEONS have come to employ the word "closure" loosely and inaccurately. It is significant that the medical dictionaries do not include the word "closure." The term is clearly defined in standard dictionaries as "act of closing or shutting; that which closes or shuts."

The misuse of the word is particularly glaring in the numerous articles on wound closure written during the recent great war and following its happy conclusion. Some authors have gone so far that they describe closure of war wounds by the three methods of undermining, swinging flap grafts and split-thickness grafts. Other authors have described wound closure by the use of split-thickness grafts alone.

The purpose of this paper is to set forth the possibilities of wound closure anatomically and physiologically by two ancient surgical procedures, namely, the radical undermining of wound margins and interpolation. Interpolation is defined as the surgical transplantation of tissue.

Many thousands of war wounded returned to our hospitals were received with wounds quickly covered by split-thickness skin grafts. These cases have proven to be a great problem, and they are with us yet. In these cases definitive surgery was not permissible since the "successful takes" had broken down and such procedures as bone grafting, arthroplasty, neurolysis, and nerve repair could not be safely carried out. What appeared to be a quick "closure" has resulted in a great delay, inasmuch as Plastic Centers had to be established and the wounded transferred to these Centers for wound closure before wound repair could be accomplished. These delays in the restoration of function could have been avoided if the wounds had been closed early instead of merely covered.

In dealing with approximately 11,000 battle wounded, all wounds were closed by excision of the wounds, the radical undermining of the margins, and the employment of marginal flaps when necessary. Epithelial grafts were not employed except in the treatment of extensive burns which, fortunately, proved to be of small incidence.

Wound closure by the methods to be presented in this paper was carried out as early after injury as covering with grafts could be safely carried out. Less time was consumed in the closure than is normally required for the use of split-thickness skin grafts. By closure of wounds with adjacent full-thickness skin and superficial fascia a functional restoration was promptly obtained, and this permitted definitive surgery as soon as wound healing occurred.

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

WOUND CLOSURE WITHOUT GRAFTS

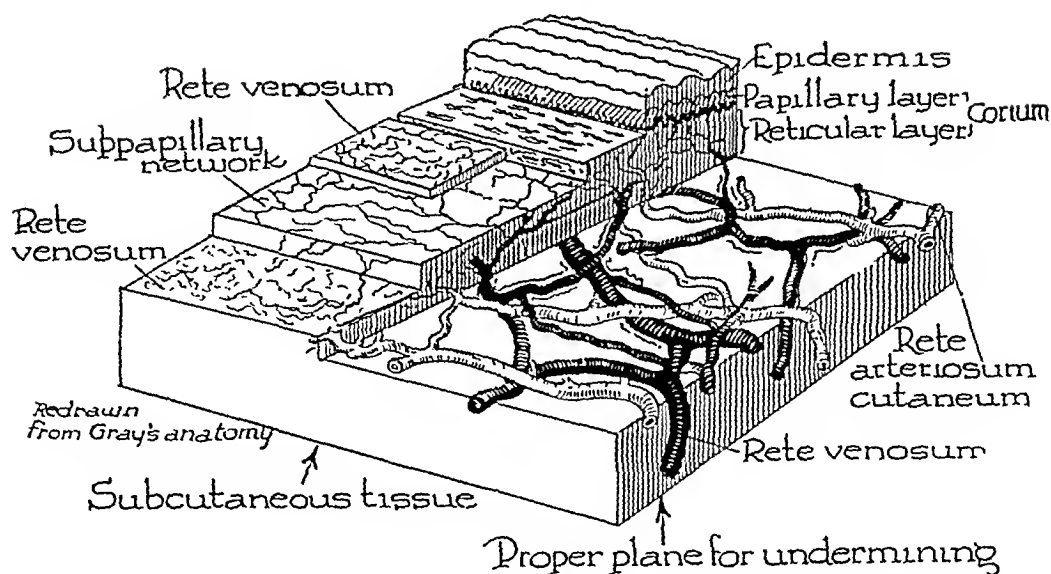


FIG. 1.—Anatomic diagram (redrawn from Gray's Anatomy, after Spalteholz) showing origin and distribution of blood supply to the skin.

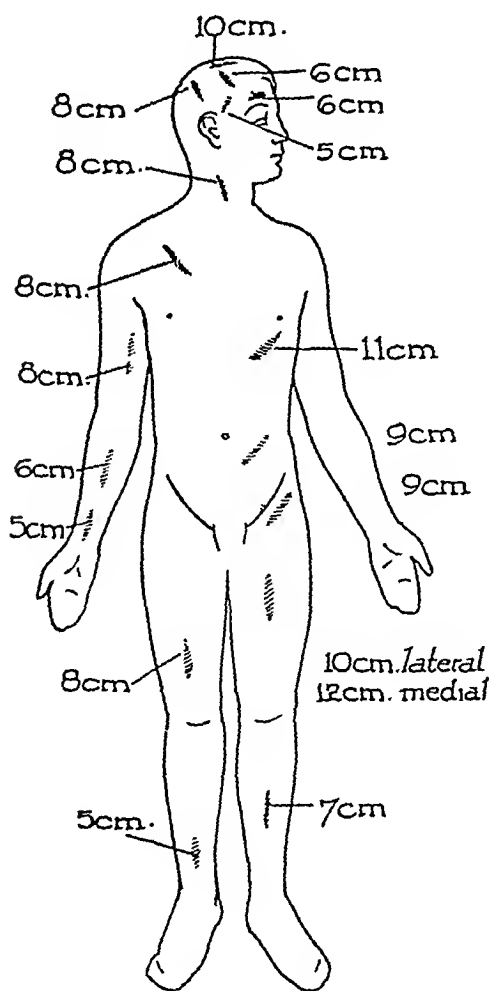


FIG. 2

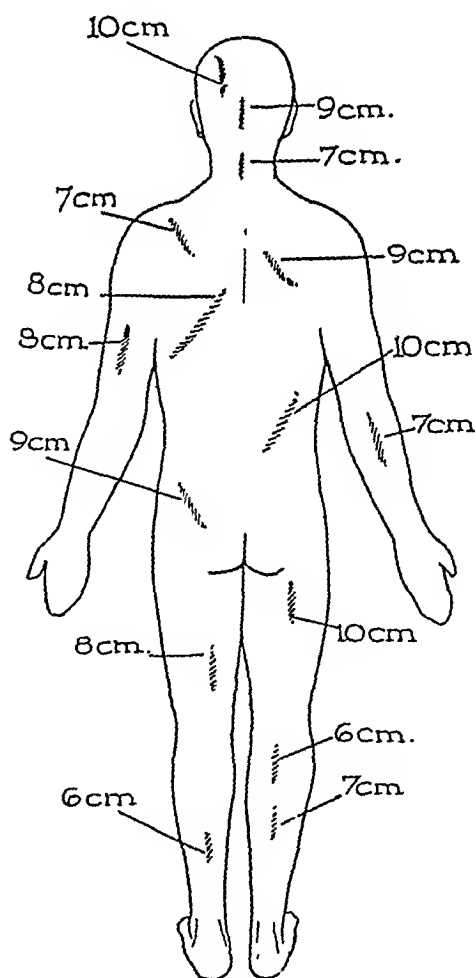


FIG. 3

FIG. 2.—Anatomic diagram (original) illustrating distances proven safe for radical undermining on anterior aspect of the body. (Not maximal)

FIG. 3.—Illustrating distances proven safe for radical undermining on posterior aspect of the body. (Not maximal)

These distances are not offered as the maximal and may well be exceeded in experienced hands.

Failure to appreciate the possibilities of wound closure by radical undermining and the use of marginal flaps has resulted in too timid employment of these methods. Fomon¹ in commenting on contiguous flaps states: "Although the principle governing this method originated in antiquity, its modern usage dates from 1830, when Larrey reintroduced it in Europe where it immediately gained popularity in the hands of such famous surgeons as Delpech, Dupuytren, Lisfranc, and Serre, and became known as the 'French flap.' While this

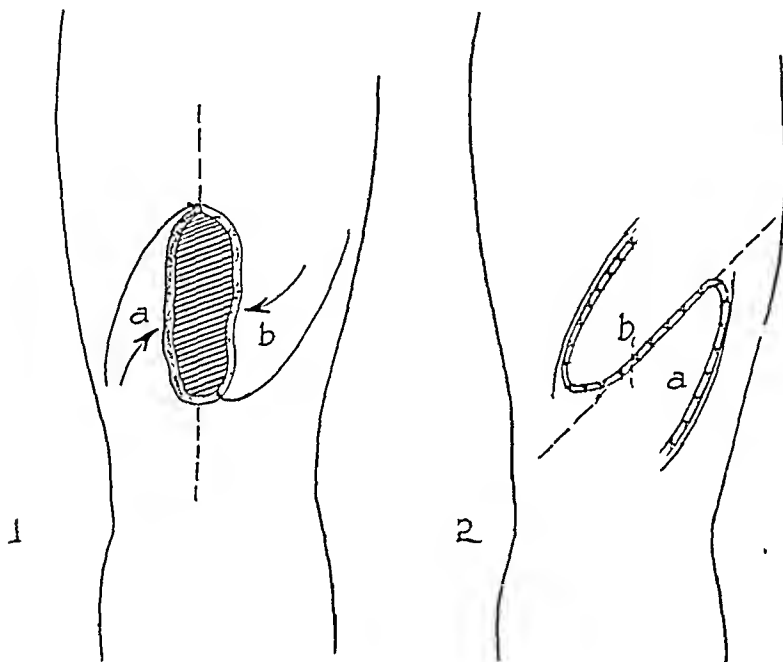


FIG. 4.—Diagrammatic illustration of interpolated marginal flaps with transposition. This affords closure by centripetal pull on margins, changing axis of the wound.

Note: The included angles of the cut marginal flaps must not be less than 20 degrees; nor greater than 45.

method has the advantage of simplicity, it is applicable only for minor defects and those in which the surrounding tissues are sound and sufficiently lax to permit of manipulation. In the case of large defects it would cause too great a distortion of the surrounding parts to warrant its use." This author, like most authors, has contributed to the failure to attempt wound closure by the employment of marginal flaps.

The skin is the largest organ of the body; it serves many important functions and comprises an area of 10 to 18,000 square centimeters; yet it does not possess an intrinsic blood supply. The skin derives its blood supply from the rete arteriosum and venosum which ramifies in the subcutaneous fascia and fat, and the subcutaneous fascia and fat, in turn, receives its blood supply

WOUND CLOSURE WITHOUT GRAFTS

from the perforating vessels arising in the deep structures² (Fig. 1). The circulation of the skin consists of capillary branches of the rete arteriosum and venosum extending into its subpapillary layers. Undermining of the skin cannot be carried out to any extent without depriving the skin of its blood supply.



FIG. 5.—Case 1: Gunshot wound, right shoulder, 15 days duration. Single-stage closure by radical undermining with reconstruction of acromioclavicular joint. Healing 10 days.

Radical undermining of the wound margins can be safely carried out to a great extent if the undermining is conducted in the proper plane for mobilization. This plane is beneath the subcutaneous fascia and fat in every anatomic location. It is imperative not to injure the perforating vessels. This procedure is not difficult if the margins are elevated, and the mobilization is carried out by divulsion with scissors rather than by cutting; and if performed under direct vision. Hemostasis is not a problem; hematomata do not appreciably occur; and greater distensibility of the wound margins is obtained. This simple

procedure will, in itself, permit the closure of larger wounds than will slight undermining in an improper plane and pulling with sutures.

A search of the literature fails to give the distances to which undermining of the margins can be carried out safely. The anatomic diagrams (Figs. 2 and 3) illustrate the distances proven safe to undermine in the various anatomic

A



B

• FIG. 6.—Case 2: Gunshot wound, severe, groin, scrotum, testicle and perineum, with transection of membranous urethra; 29 days duration. Single-stage closure by radical undermining, with repair of scrotum, testicle and urethra. Healing completed 14 days.

locations. These distances are not offered as the maximum which can be attained, and could well be exceeded in experienced hands.

In wounds that do not permit of closure after radical undermining, multiple-stage closure is practicable and repeated undermining and closure can be carried out at intervals as early as two weeks. Compensatory relaxation occurs

WOUND CLOSURE WITHOUT GRAFTS

within that period and continues for months. Otto,³ in dealing with subtotal avulsion of the scalp, has shown what can be accomplished by this method.

The second simple surgical procedure to be executed in wound closure without the use of grafts is the employment of marginal flaps. In wounds that cannot be closed after radical undermining because tension is too great across



FIG 7.—Case 3: Gunshot wound, arm, left, medial aspect; 17 days duration. Single-stage closure after radical undermining, with rotation of single marginal flap. Complete healing 7 days.

any given diameter, marginal flaps may be cut and rotated across the wound. This procedure affords closure by permitting of centripetal pull on the margins of the wound; it is illustrated in Figure 4. When cutting marginal flaps the included angle formed by the margin of the wound and the incision should not be less than 20 degrees. This insures circulation to the tip of the newly-formed flap. Nor should the angle be greater than 45 degrees to enable rotation across the denuded surface. The size and the number of marginal flaps to be employed is determined by the size of the wound to be closed.

The technical methods of closure discussed are to be carried out only after proper preparation of the patient. Shock must have been combatted, anemia

and hypoproteinemia corrected, blood serum level restored to normal, avitaminosis reduced and general and local sepsis controlled. The methods of accomplishing these results are too well-known to warrant repetition in this paper. The importance of carrying out this preparation of the patient cannot be overemphasized since normal wound healing does not occur if they are neglected.

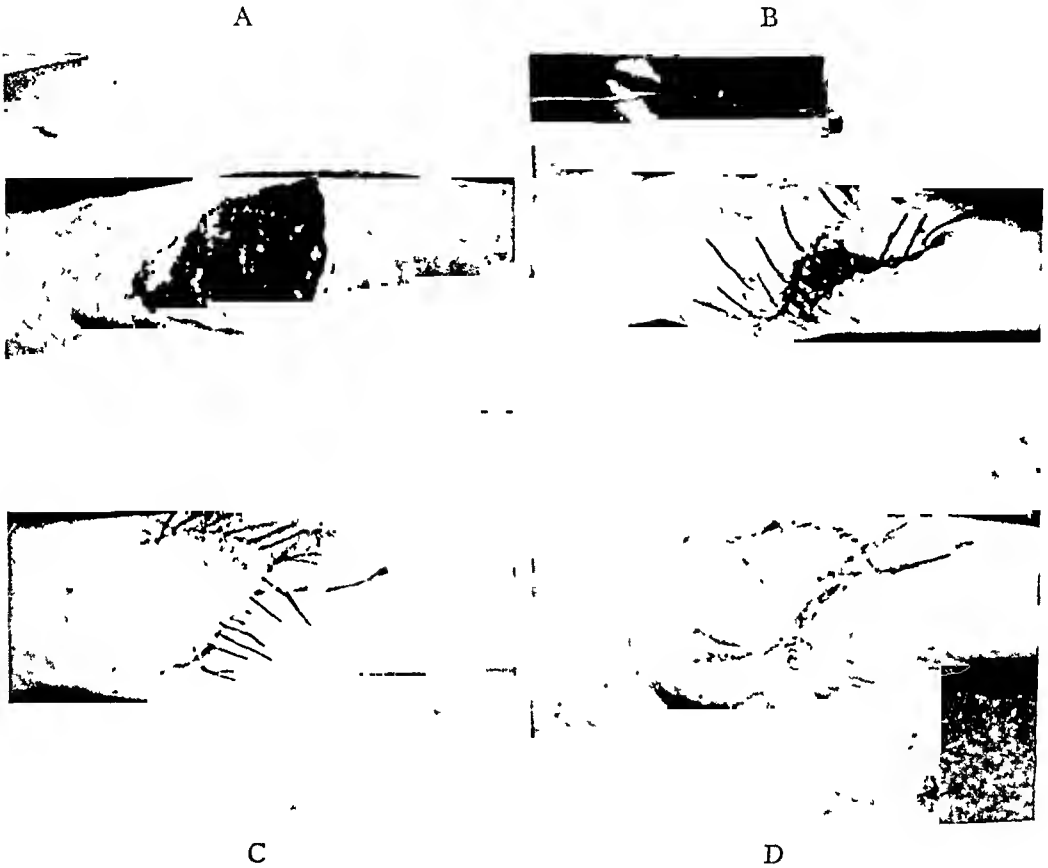


FIG 8.—Case 4: Gunshot wound, leg, right, posterior aspect; subtotal loss of gastrocnemius and compound comminuted fracture fibula; duration 26 days. First stage: partial closure after radical undermining, with single marginal flap. Second stage: 14 days later, repeated radical undermining with complete closure. Complete healing 24 days.

Épluchage is the French term for complete excision of a wound. It demands a greater wound revision than simple débridement. In surgical preparation of wounds for closure by the described methods, épluchage is carried out. The skin margins are cut away vertically five to six millimeters proximal to the border of granulation. All granulation tissue is carefully removed by excision and curettage, since it is to be regarded as infected tissue and young scar tissue. Granulation tissue, the early tissue of wound repair, is young connective tissue. It consists primarily of capillary loops surrounded by fibroblasts which fuse with each other. The fibroblasts contract progressively to the

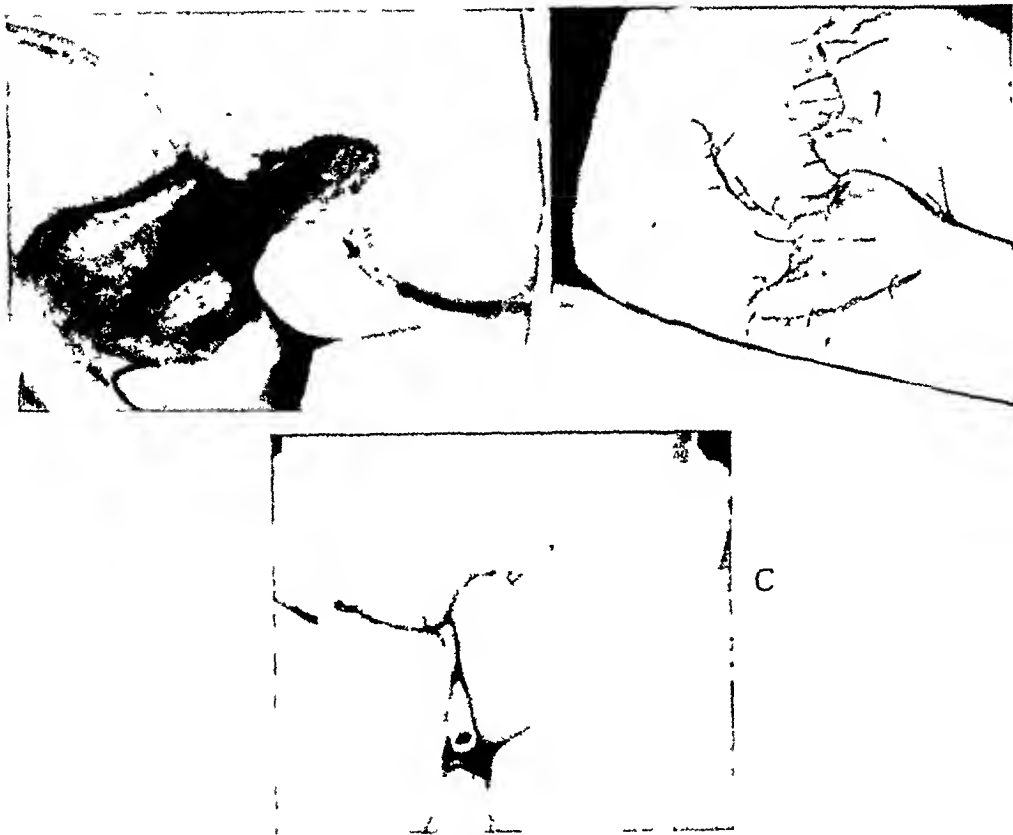


FIG. 9.—Case 5: Shell fragment wound, severe, buttock, with loss of rectum, coccyx and lower sacrum; duration 63 days. Single-stage closure by radical undermining, with utilization of three marginal flaps. Devine colostomy previous to closure. Complete healing 14 days. Followed by reimplantation of rectum 17 days after first stage.

A

B

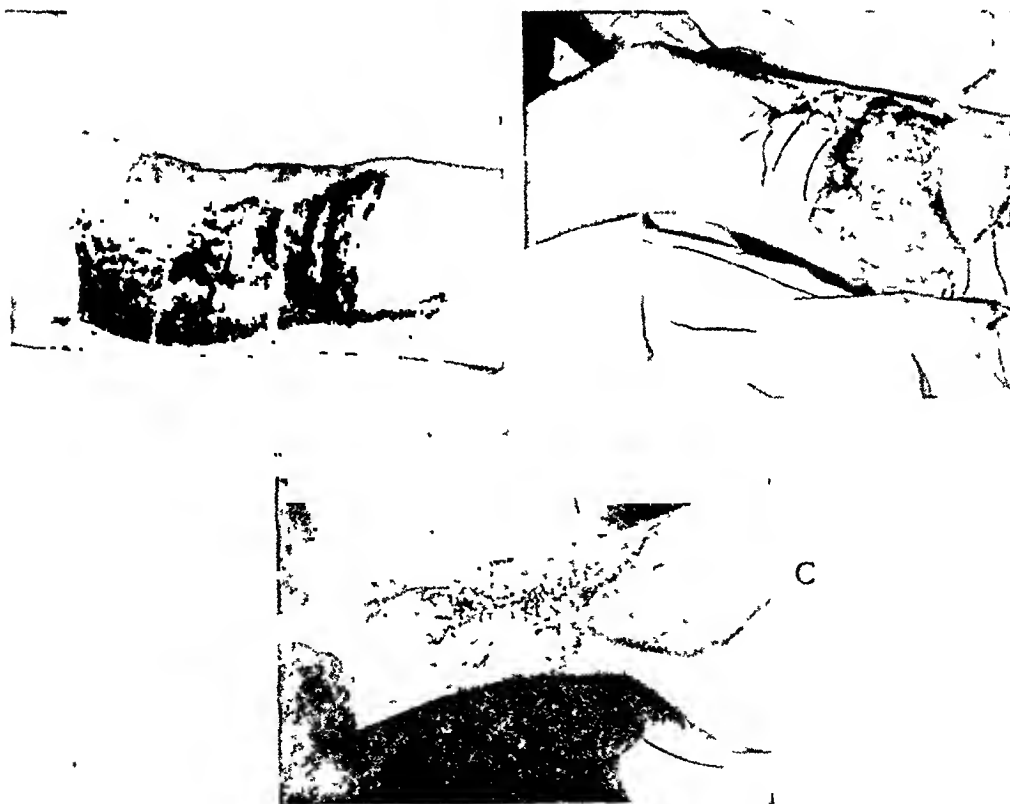


FIG. 10.—Case 6: Shell fragment wound thigh, left, posterolateral aspect, with extensive loss of vastus lateralis and hamstring muscles; duration 39 days. First stage: partial closure by radical undermining and two marginal flaps. Second stage: 15 days later, radical undermining and employment of marginal flap from posteromedial aspect of thigh. Third stage: 17 days later, radical undermining and employment of marginal flap from gluteal region. Fourth stage: 30 days later, radical undermining of margins and closure completed. Total elapsed time for closure and healing, 73 days.

formation of scar tissue which becomes increasingly avascular if left in the wound.

In the approximation of the freshly cut margins after mobilization and interpolation, sutures are to be used judiciously. Tension sutures are spaced three to four centimeters and include two to four centimeters of the flap. Skin approximation sutures are spaced one and one-half centimeters, and are alternately of the end-on mattress type to prevent inversion and eversion. They should be placed 15 to 20 millimeters from the wound margins. In large wound closures small Penrose drains have been employed. Compression bandages with elastic wrapping are applied to control oozing and to splint the tissues. When indicated, plaster splints are used for immobilization.

Closures accomplished by these methods are shown photographically in Cases 1, 2, 3, 4, 5 and 6.

SUMMARY AND CONCLUSIONS

1. Secondary closure of wounds is possible in the vast majority of cases if the principles discussed are thoroughly understood and carried out.

2. Simple surgical procedures applicable for secondary wound closure without grafts are reviewed.

3. Multiple-stage closures can be safely employed.

4. Results of secondary wound closure by these methods restores normal functions, and permits of definitive surgery in a shorter elapsed time.

5. The diagrams (Figs. 2 and 3) show the distances proven safe for mobilization in different anatomic locations.

6. The advantages of wound closure without the use of grafts has been rationalized.

REFERENCES

- 1 Fomon, Samuel: *The Surgery of Injury and Plastic Repair*. The Williams and Wilkins Company, Baltimore, 1939. Pp. 233-240.
- 2 Gray's Anatomy, Lewis, Edition 24, P. 1085 (after Spalteholz).
- 3 Otto, T. O.: Avulsion of the Scalp Treated without Grafting. *ANNALS OF SURGERY*, 102, 315, August, 1935.

DISCUSSION.—DR. JOHN STAIGE DAVIS, Baltimore, Md.: Doctor Otto's paper has brought to our attention, again, the very important fact that many extensive wounds can be closed without the use of skin grafts. Since the development of the dermatome, skin grafting has been done by many men who could not previously cut a graft, and it has been thoroughly overworked. Skin grafting has been done in many cases where it should not be done. I should say that, roughly speaking, 50 per cent of the wounds that are skin grafted could be closed by some such method as has been demonstrated by Doctor Otto. It is well to realize that skin-closing and wound-covering with grafts are different things, and the latter frequently leaves an area very difficult to deal with and one which it not functionally satisfactory. A wound closed by suture of the subcutaneous tissue and the skin always gives a very much better functional result.

DR. ROBERT IVY, Philadelphia, Pa.: I wish to thank the Association for inviting me to the meeting and allowing me the privilege of discussing Doctor Otto's excellent paper.

I am in entire agreement with him and with Dr. Staige Davis about closure of these wounds by undermining the local skin and subcutaneous tissue whenever possible, without the use of skin grafts. In some extensive wounds, too large to be closed by this method, a marginal flap can be used, and the raw area that is left by sliding over the flap can then be covered by a skin graft, so that the graft will not be on the site of the original wound. Doctor Otto spoke of the frequency with which grafts used on these wounds break down, but even though they heal well they do not provide a satisfactory soft tissue bed for later orthopedic or neurosurgical procedures.

In the correction of scars and lesions about the face where the cosmetic result is important, the use of local tissues by undermining and formation of sliding flaps, after multiple excision of the scar or growth, has been emphasized by Ferris Smith in preference to covering the raw areas with grafts, which may be unsightly and many times do not provide the proper contour.

DR. J. ALBERT KEY, St. Louis, Mo.: I am very happy to hear this paper, because many young surgeons in the Army who had dermatomes had to use them, and they did use them. Everything that could be grafted was grafted. They are getting to be the same in civil life.

There is another factor besides the dermatome which has led to an epidemic of skin grafting; that is, the undue emphasis put on never closing a wound with tension. The reason we have strong suture material is to pull them tight when necessary. It is amazing, if you strip a flap from the deep fascia by blunt dissection, how much stretch can be obtained. That is not good surgery to some of you people, but it works. We should get away from this idea of not suturing wounds with tension.

DR. THOMAS O. OTTO, Miami Beach, Florida (closing): I want to thank Doctor Davis, Doctor Ivy and Doctor Key for discussing my paper. Doctor Key's use of blunt dissection for undermining, rather than undercutting, conserves the peripheral blood supply. One must undermine beneath the subcutaneous fascia and fat if the blood supply to the skin is to be conserved.

BILATERAL CUTANEOUS URETEROSTOMY EIGHTEEN YEARS AFTER URETEROSIGMOIDOSTOMY FOR EXSTROPHY OF THE BLADDER*

EDGAR BURNS, M.D., W. E. KITTREDGE, M.D., AND
JACK HYMAN, M.D.

NEW ORLEANS, LA.

FROM THE DEPARTMENT OF SURGERY, TULANE UNIVERSITY SCHOOL OF MEDICINE
AND THE DEPARTMENT OF UROLOGY, OCHSNER CLINIC, NEW ORLEANS, LA.

URETERO-INTESTINAL ANASTOMOSIS has been utilized as a means of diverting the urinary stream in exstrophy of the bladder and a variety of other incapacitating vesical lesions. Since Simon¹ first suggested and carried out uretero-intestinal anastomosis for exstrophy of the bladder in 1815, numerous methods for performing the operation have been devised. Original technics have been modified many times in an effort to obtain more satisfactory results. The age at which operation is performed is thought to bear some relationship to the complications which arise from ascending infection of the kidneys. The present tendency is to operate early, preferably within the first six months of life, before the bacterial flora of the bowel become too varied and pathologic. Higgins² reported 17 cases of infants operated upon when less than one year of age. He felt that the incidence of pyelonephritis in this group was less than if the operation had been deferred until an older age. Two of the 17 died during the postoperative period. The age at which the operation is performed does not, of course, eliminate such mechanical factors as angulation and stricture formation at the site of anastomosis, factors which most likely account for the majority of complications encountered in these cases.

From a review of the literature it is difficult to determine the percentage of patients who remained well for a period of years after ureterosigmoid anastomosis. In the majority of reports, statements as to the general health of the patient are vague and data concerning renal function tests are not sufficient to be helpful. By combining the reports of 13 authors³⁻¹⁵ we were able to collect 41 cases of uretero-intestinal anastomosis in which the status of the patient could be evaluated (Table I). An analysis of the 41 collected cases, and our own case, revealed that these patients were alive from six to 44 years after operation. Sixteen patients, or 38 per cent, were reported as "well" and by "well" we assume that there was no clinical evidence of renal infection or insufficiency. In the remaining 26 cases, or 62 per cent, the following conditions were encountered: hydronephrosis, 21 times; loss of function of one kidney, eight times; renal calculi, seven times; calculous pyonephrosis necessitating nephrectomy, two times; and infected hydronephrosis requiring

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

CUTANEOUS URETEROSTOMY

TABLE I

ANALYSIS OF 41 CASES OF URETERO-INTESTINAL ANASTOMOSIS

Collected from the Literature

Author	Age at Op. Years	P. O.	Status of Urinary Tract
Estor ² (1926)	1 5/12	24	Well
Middleton ⁴ (1931)	17	20	Blood urea nitrogen 32 mg. $\%$. Urograms mild hydronephrosis.
Walters ³ (1932)	25	15	I. V. urograms normal. Blood urea nitrogen normal.
Foulds ⁶ (1933)	4	26	19 yrs. postop. Right calculus pyonephrosis and perinephric abscess. Left renal calculus passed spontaneously, with rupture of lower ureter and death. Blood urea nitrogen 83.7 mg. $\%$.
	11	25	Well
Allison ⁷ (1933)	7	20	Blood urea nitrogen 26 mg. $\%$. Left calculus. Pyonephrosis and perinephric abscess. Dead left kidney.
Estes ⁸ (1934)	5	22	Died in uremia—Autopsy: Contracted kidney; Thickened ureters.
Falk ⁹ (1938)	7	25	Right nephrectomy for pyonephrosis—Left kidney normal.
Fisher ¹⁰ (1948)	16	22	Blood urea nitrogen 91 mg $\%$ —Died—Autopsy: Bilateral pyonephrosis and pyoureter.
Wade ¹¹ (1939)	3	35	Renal function tests and I. V. urograms normal.
	10	28	Left renal calculus passed spontaneously. Blood urea 48 mg. $\%$.
	27	12	Hydronephrosis and hydroureter.
	17	13	I. V. urograms showed normal function.
Hepler ¹² (1940)	8	15	All living and well—by well, author states patient is healthy, has no clinical evidences of persistent renal infection or insufficiency and no marked changes in the ureters or kidney pelves.
	7	15	
	5	14	
	6	13	
	38	14	
Stevens ¹³ (1941)	36	11	
	16	26	NPN 38, PSP 1 hr. 25%. Marked left hydronephrosis. 2 episodes of infection requiring bed care.
	22	7	Recurrent urinary infection. Died.
	49	11	NPN 53. PSP 10% 1 hr. Right hydronephrosis.
	28	6.5	NPN 35. PSP 20% 1 hr. Urograms dilatation rt. ureter pelves. Left incompletely outlined.
	15	11	NPN 34. PSP 45% 1 hr.
	36	6	Dendritic calculus. NPN 128. Died.
	6	44	Renal calculus. Died.
Turner ¹⁴ (1943)	8	30	Apparently well.
	22	29	Calculi requiring removal 24 yrs. after.
	19	25	Apparently well.
	6	25	Right renal calculus removed 14 years after.
	5	23	Renal pain 22 years after.
	10	19	Apparently well.

TABLE I—*Continued*

Author	Age at Op. Years	P. O.	Status of Urinary Tract
Lower ¹³ (1943)	8.5	17	Nephrectomy for pyonephrosis.
	3	16	Apparently well.
	3.5	16	Apparently well.
	10	22	Recurrent renal infection. Blood urea 48 mg. %.
	3.5	18	Blood urea 51 mg. %. Left hydronephrosis. Dilatation of right ureter.
	23	21	45-minute urograms. Right hydronephrosis. Left excreted very little dye. Blood urea 51 mg. %.
	22	21	Blood urea 42 mg. %. Urograms showed normal renal pelvises.
	30	18	Nonfunctioning right kidney. Blood urea 54 mg. %.
	18	27	Normal right kidney with right hydroureter. Left kidney fails to visualize. Blood urea 54 mg. %.

nephrostomy, two times. These conditions obviously assume the same importance as they do when encountered in individuals who have an otherwise normal urinary tract. Defective drainage from cicatricial stenosis of the intestinal anastomosis is largely responsible for the late appearance of dilated ureters, hydronephrosis, recurrent infections, stone formation and impaired renal function encountered in these cases. The pronounced dilatation of the ureters precludes reimplantation to the sigmoid, so that cutaneous anastomosis appears to us the most desirable alternate.

If the small series of cases evaluated above constitutes an index to the whole picture, it is apparent that the late results in more than half of these cases are unsatisfactory. In this report we are chiefly concerned with this group. It is our purpose to show that the life expectancy of certain patients selected from this group may be improved by uretero-cutaneous anastomosis and to report such a case.

Case Report.—C. D. M., a 30-year-old white man, was first seen in the Ochsner Clinic, August 20, 1945, with the chief complaints of renal discomfort and recurrent chills and fever.

At the age of 12 years bilateral uretero-intestinal anastomosis (Coffey-Mayo operation) was performed by Dr. C. H. Mayo for exstrophy of the bladder. One year following the operation the patient began to have pains in the left flank associated with nausea, chills and fever. These symptoms subsided when the patient was given a purgative. They recurred, however, at intervals of about six months. These episodes continued until the early part of 1940, when the left-sided renal pain subsided and has not recurred. At about this time, however, the patient began to have pain in the right side associated also with chills and fever. His capacity for work during the past five years has become increasingly limited.

A year before the patient consulted us his local physician made an excretory urogram which was said to show the right kidney and ureter to be in good condition but the left kidney and ureter were not visualized. At that time, specimens of urine obtained from the rectum revealed pus but no blood. The patient was given sulfonamides and mandelic acid, which had no tendency to control the acute episodes of urinary infection. Instead,



FIG. 2.—Forty-minute excretory urogram on admission revealing right hydronephrosis with hydro-ureter and only faint trace of dye on the left.

CHEN CLINIC
FEB 24 1952



FIG. 1.—Plain roentgenogram on admission revealing calculus in left kidney.

CHEN CLINIC
FEB 24 1952

they recurred with increasing frequency. The most recent attack occurred two weeks before we saw him and was characterized by pain in the right flank, chills and fever.

The patient was able to have intercourse with difficulty but has ejaculations. His appetite was fair and bowel movements were regular.

The patient was a well-developed, fairly well-nourished, intelligent white male, somewhat pale but not acutely ill. He weighed 135 pounds. At examination, both kidneys were palpable, and the right was moderately tender. Three scars from previous operations marked the lower part of the abdomen. There was complete epispadias. Rectal examination disclosed no mass which could be identified as prostatic tissue.

Examination of the blood revealed 5,300,000 red blood cells, 15.5 Gm. hemoglobin, 8,400 white blood cells, 75 per cent segmented cells and 25 per cent leukocytes. Blood urea nitrogen was 20 mg. per cent.



FIG. 3A.—Mathé collecting apparatus in position on the patient.

Plain roentgenograms of the urinary tract showed a calculus, measuring 4 cm. in length by 0.5 cm. in width, in the left renal pelvis (Fig. 1). The excretory urograms revealed slow concentration of the diodrast on the right side and showed a fair outline of the pelvis and calices in 40 minutes disclosing blunting of the calices and marked dilatation of the pelvis and ureters (Fig. 2). The left kidney showed only a faint trace of the dye in the forty-minute film.

The patient was put on a maintenance dose of mandelic acid in an attempt to control the urinary infection. He returned in two months for reexamination and reported that he had not had fever in the interval. Excretory urograms showed no change from the previous films. The blood urea nitrogen had risen to 25 mg. per cent, and the patient had lost five pounds in weight.

It was felt that surgical intervention was indicated in order to remove the obstruction to drainage at the site of anastomosis. Accordingly, November 26, 1945, bilateral cutaneous ureterostomy was done. Under spinal anesthesia a right lateral abdominal incision was made, the old scar being excised. The muscle and fascia were divided and the peritoneum with its contents was retracted medially. The right ureter was found to be about 2.5 cm. in diameter, with a very thin, almost transparent wall. There was

CUTANEOUS URETEROSTOMY

little evidence of periureteritis. As the ureter approached the peritoneum, it narrowed down considerably, and there were dense adhesions around this junction. These were not disturbed. The ureter was divided just outside the peritoneum. The distal stump was ligated with a transfixed No. 2 chromic catgut suture and the proximal stump was freed

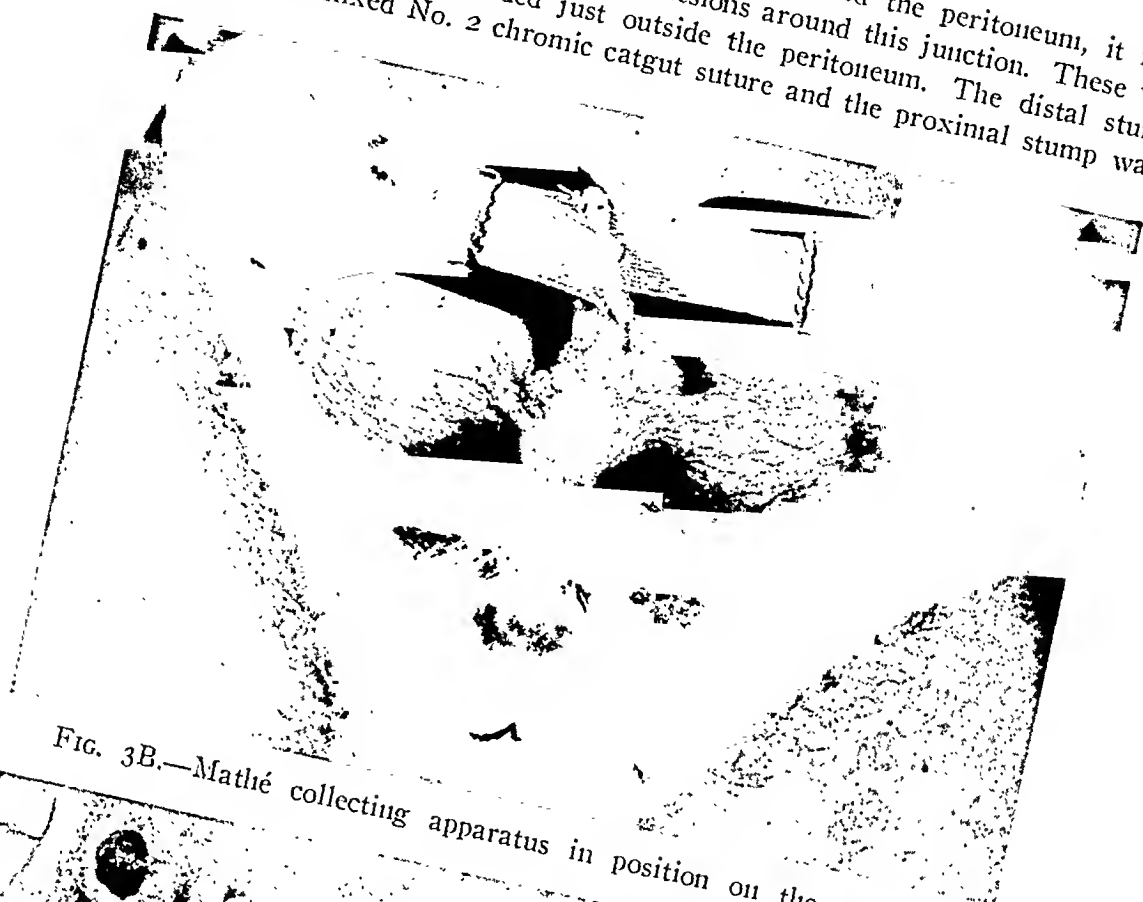


FIG. 3B.—Mathé collecting apparatus in position on the patient.

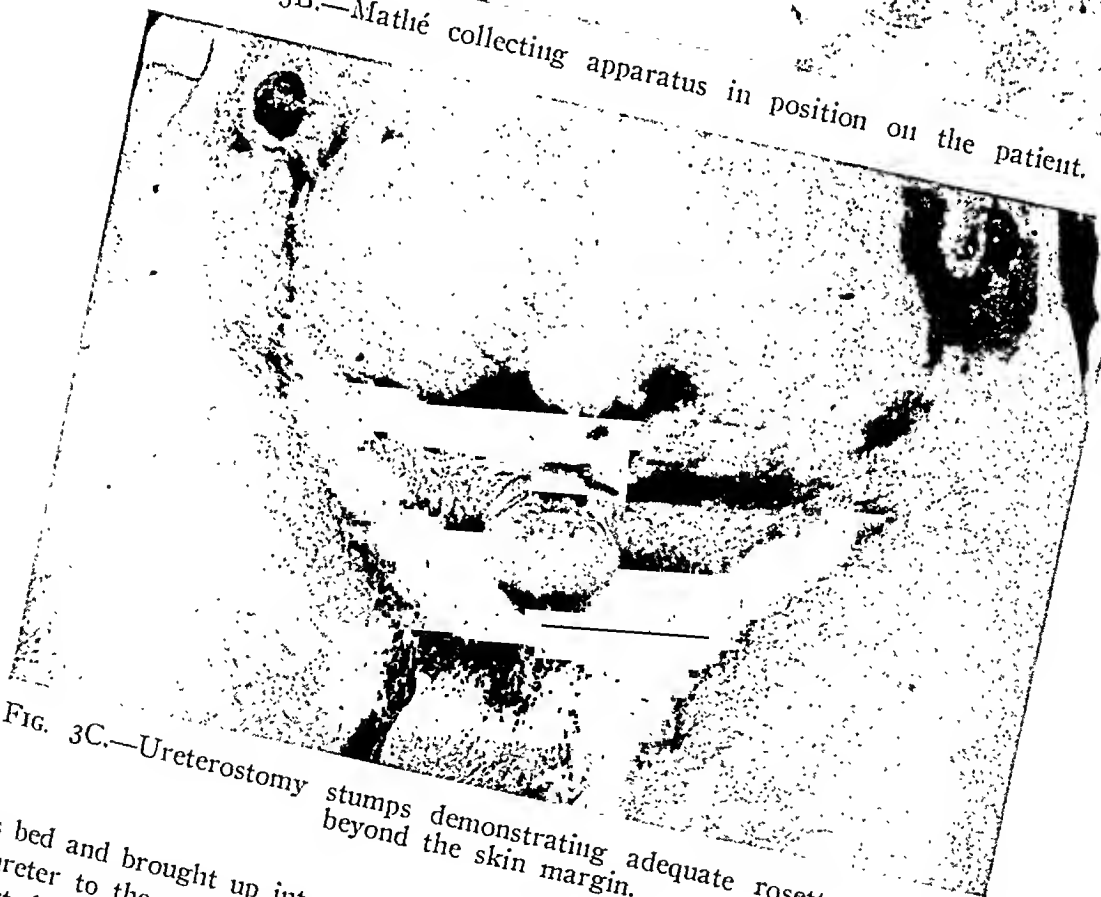


FIG. 3C.—Ureterostomy stumps demonstrating adequate rosette of ureter beyond the skin margin.

from its bed and brought up into the wound. A No. 16 Robinson catheter passed easily up the ureter to the renal pelvis. This catheter was left in place. One Penrose drain was inserted into the lower angle of the wound, and the wound was closed in layers, with catgut for muscle and fascia and silkworm and dermal for the skin, care being exercised

not to constrict the ureter. No difficulty was encountered in obtaining a good length of ureter beyond the skin margin.

A similar procedure was carried out on the left side. The ureter was about 2 cm. in diameter and not particularly distended. Only a little urine escaped when it was opened. There was also very little periureteritis on this side. The ureter was severed close to its peritoneal entrance, the distal stump was transected as on the right, and the proximal stump was freed from its bed and brought up into the wound. A long stone forceps was easily introduced up the ureter to the renal pelvis in an attempt to remove



FIG. 4.—Excretory urogram five months after operation revealing considerable improvement in hydronephrosis and concentration of dye.

the stone noted in the plain roentgenogram. This could not be accomplished, however, as the stone had slipped down into the lower calix. A No. 16 Robinson catheter was passed up to the kidney with ease, and left in place. The wound was closed, the ureteral stump being brought well beyond the skin surface as on the right. The patient's post-operative course was uneventful. It was noteworthy that at first only about one-sixth as much urine was excreted from the left kidney as from the right. The ureteral stumps healed excellently.

Approximately two weeks after the operation an indigo carmine test was done; the dye, injected intravenously, appeared from the right ureter in excellent concentration in three minutes, and from the left ureter in ten minutes in about 50 per cent of the normal

concentration. The patient was fitted with a Mathé-type of collecting apparatus and discharged from the hospital (Fig. 3a, 3b, 3c). His ureters were functioning well and retention ureteral catheters were not required.

The patient reported for a check-up five months after the operation. During this interval, he had gained 15 pounds in weight. His general health had improved, and he was entirely free of urinary symptoms. Excretory urograms at this time revealed a great reduction in the size of the hydronephrosis on the right side, with some improvement of function (Fig. 4). There had been considerable increase in excretion of the dye on the left, which indicated improvement of function of the left kidney. There had, likewise, been an increase in the size of the calculus in the left kidney which, in itself, is



FIG. 5.—Excretory urogram 11 months after operation revealing further improvement in hydronephrosis and in concentration of dye by both kidneys.

indicative of improved renal function. On July 5, 1946, the stone was removed from the left kidney, and recovery was uneventful.

The patient reported for reëxamination October 15, 1946. His general health was excellent. His weight was 160 pounds, a gain of 25 pounds over his weight on admission. He was doing full-time work as a bank clerk, and during the summer season was the pitcher for his local softball team. Excretory urograms showed further improvement in the function of the kidneys (Fig. 5).

DISCUSSION.—The advantages expected to be derived from transferring the ureters to the skin in this case were (1) relief of back pressure on the kidneys; (2) control of urinary infection; (3) improvement of renal function; and (4) restoration of the patient to economic usefulness. All of these were accomplished and, in addition, we were able to prevent some of the disagreeable features often associated with cutaneous ureterostomy. The patient's ureters function well without catheters. He wears his apparatus with comfort, and is able to keep dry during both day and night.

One of the most unfortunate complications of cutaneous ureterostomy is to have the end of the ureters slough down to, or below, the skin margin. In such cases disagreeable strictures form. These are painful and hard to keep open. On one or two occasions we have immediately dissected down to viable ureter and brought it out to a higher level in order to get a good length beyond the skin surface. This may not be possible in all cases and nephrostomy may occasionally be required. Attempts are always made to prevent this complication by the observation of several well-recognized rules. The ureter should be freed from its bed without stripping in order to avoid injury to its blood supply. It is brought out without tension or angulation and allowed to project 4 to 5 cm. beyond the skin margin. The wound is closed lightly around the ureter and no stitches are placed in the ureteral wall. A suture in the ureteral wall will damage the blood supply and is not necessary if the length of ureter is adequate. The catheter used during the immediate postoperative period should be small enough to fit loosely in the ureteral lumen.

With respect to prognosis following ureterocutaneous anastomosis there is a scarcity of such reports in the literature. However, Keyes^{16, 17} reported cases of patients living from 13 to 22 years after cutaneous ureterostomy for intractable tuberculosis of the bladder. Other similar reports may be found. It is reasonable to assume that the prognosis of more benign lesions would be equally as good. We are not suggesting that cutaneous ureterostomy will be indicated in a large number of cases following uretero-intestinal anastomosis. However, a review of the literature reveals that in many patients severe urologic lesions develop in the years subsequent to uretero-intestinal implantation. We believe that relief of the mechanical obstruction at the terminal end of the ureters by transferring the ureters to the skin will undoubtedly prolong the life of many of these patients.

SUMMARY

The literature on the late results of uretero-intestinal anastomosis has been reviewed in an attempt to evaluate the renal status in patients many years after operation. It is suggested that detachment of the ureter from the sigmoid and reimplantation into the skin as a means of relieving mechanical obstruction to the urinary flow will prolong life in the late stages of uretero-intestinal anastomosis. Such a case is reported.

REFERENCES

- ¹ Simon: Quoted by Hinman, F.: Principles of Urology. Philadelphia, W. B. Saunders, 1935, P. 991.
- ² Higgins, C. C.: Transplantation of the Ureters into the Rectosigmoid in Infants: Review of 19 Cases. Tr. Am. A. Genito-urin. Surgeons (1943), 36, 267, 1944.
- ³ Estor, E.: Exstrophy of the Bladder: Junction of the Ureters with the Upper Part of the Rectum: Results 24 Years after Operation. J. d'Urol., 22, 242, 1926.
- ⁴ Middleton, G. W.: Submucous Ureteral Implantation into Bowel: Twenty-Year Report on First Human Case. J. A. M. A., 97, 1536, 1931.
- ⁵ Walters, W.: Transplantation of Ureters to Rectosigmoid and Cystectomy for Exstrophy of Bladder. Am. J. Surg., 15, 15, 1932.
- ⁶ Foulds, G. S.: Historical Data on Ureteral Transplantation. Am. J. Surg., 22, 217, 1933.
- ⁷ Allison, P. R.: Result of Transplantation of Ureters more than a Quarter of a Century after Operation. Brit. J. Surg., 20, 529, 1933.
- ⁸ Estes, W. L.: Exstrophy of the Urinary Bladder. ANNALS OF SURGERY, 99, 223, 1934.
- ⁹ Falk, R., and Smith, R. S.: Nephrectomy 25 Years after Ureterosigmoid Anastomosis: Instance of Pneumopyonephrosis. Northwest Med., 37, 353, 1938.
- ¹⁰ Fisher, J. H.: A Case of Ureteral Transplantation (Peter's Operation) Surviving 22 Years. Brit. J. Urol., 10, 241, 1938.
- ¹¹ Wade, H.: The Expectancy of Life after Ureteral Transplantation (Honyman Gillespie Lecture), Edinburgh M. J., 46, 61, 1939.
- ¹² Hepler, A. B.: End-results of Uretero-intestinal Implantation. J. Urol., 44, 794, 1940.
- ¹³ Stevens, A. R.: Longevity following Uretero-intestinal Anastomosis: Report of Cases. J. Urol., 46, 57, 1941.
- ¹⁴ Turner, G. G.: Transplantation of the Ureters into the Large Bowel. Brit. M. J., 2, 535, 1943.
- ¹⁵ Lower, W. E.: Late Results following Transplantation of the Ureters into the Rectosigmoid. J. Urol., 50, 581, 1943.
- ¹⁶ Keyes, E. L.: Cutaneous Ureterostomy for Relief of Intractable Bladder Tuberculosis. J. Urol., 44, 40, 1940.
- ¹⁷ Keyes, E. L.: Autopsy 22 Years after Cutaneous Ureterostomy for Tuberculosis. Tr. Am. A. Genito-urin. Surgeons (1943), 36, 181, 1944.

DISCUSSION.—DR. LEO BRADY, Baltimore, Md.: I think this is a very important and interesting contribution. Unfortunately, we do at times get in trouble after implanting the ureters into the large intestine, but as our technic has improved these complications have become less frequent. The new drugs, such as sulfathaladine, and the improvement in the operative technic have been helpful.

I should like to mention one patient whose convalescence has been very satisfactory. She had a papillary carcinoma of the bladder which did not respond to fulguration, radium or roentgen ray. I removed the entire bladder and implanted the ureters into the rectum, using the Coffee No. 2 operation. It has been four years since the operation was performed and her general condition has been excellent. There are no complications, and she voids only twice a night. The intravenous pyelogram is absolutely normal and there is no dilatation of the kidney pelves or the ureters.

Doctor Burns' paper is very instructive and helpful. In the future when I have a patient whose ureters I have implanted into the rectum and whose ureters and kidney pelves show progressive dilatation, I shall remember Doctor Burns' case.

OBITUARIES

GEORGE P. MULLER

1877 - 1917

For twelve years a member of the Editorial Board of the ANNALS OF SURGERY, Dr. George P. Muller died at his home in Margate, N. J. on February 18, 1947, following a short illness.

Doctor Muller was born in Philadelphia in 1877, and in 1899 received his medical degree from the University of Pennsylvania Medical School and



Dr George P. Muller

continued with the University through successive positions as assistant instructor, instructor associate and professor of clinical surgery until July, 1933. For 13 years during this period he was also Professor of Surgery in its Graduate School of Medicine. In 1937 he became Osler Professor of Surgery at Jefferson Medical College, which position he held until 1946. Doctor Muller served as consulting surgeon to Rush Hospital and White Haven Sanatorium, and at Lankenau and Misericordia Hospitals, and was a past president of the Philadelphia County Medical Society, the Philadelphia Academy of Surgery, the College of Physicians of Philadelphia and the American College of Surgeons.

OBITUARIES

In 1935 when the Editorial Board of the ANNALS OF SURGERY was formed, Doctor Muller joined with a group of other outstanding surgeons from all parts of the country to help maintain the publication in the honorable position established for it by its founder, Dr. Lewis S. Pilcher, whose son, James, was Managing Editor until his recent death.

As a frequent contributor to the surgical literature, Doctor Muller brought to the ANNALS OF SURGERY the sound surgical and literary ability which had long been manifest during his distinguished career. The Board and the publishers will miss his wise counsel in the selection and appraisal of articles for this publication, and acknowledge great credit to him in helping to make the ANNALS of increasing value to the student and to the growing number of young men rising into the specialty of surgery.

JAMES TAFT PILCHER

1880 - 1947

Another great loss to the Editorial Board of the ANNALS OF SURGERY was suffered with the passing of Dr. James T. Pilcher, who died at his home in Brooklyn, N. Y. of a heart attack on April 6, 1947, a day following his 67th birthday.



Dr. James Taft Pilcher

Son of Dr. Lewis S. Pilcher, founder of the ANNALS OF SURGERY, James Pilcher was Managing Editor of the publication from 1935 until his death. His devotion to the standards set up by his father and carried on by the initial

board appointed in 1935 was manifest in the keen, critical interest he brought to this work. As a surgeon with a career covering two years on the staff of the Mayo Clinic, commanding officer of the 108th Field Hospital in France during the first World War, and a practice in surgery for over 40 years in Brooklyn, Doctor Pilcher's diligence and industry in preparing papers for publication did much to make the ANNALS OF SURGERY of such increasing value to the surgical specialty. His editorial conscience was ever on the alert for uniformity and accuracy in styling, he was always eager to track down new spellings, to confirm changes in nomenclature, and to put his best surgical judgment to the task of making the pages of the ANNALS of even excellence. The contributors who depended upon him and the other editors on the Board, with whom he was so closely associated, will miss him greatly.

Doctor Pilcher received his medical education at Columbia University and was a visiting surgeon to the Wycoff Heights Hospital and Evangelical Deaconess Hospital and had been Director of Urology at Downtown Hospital, New York, and attending surgeon at the Brooklyn State Hospital and Unity Hospital. In the first World War, he held the rank of major in the Medical Corps and received the Distinguished Service Medal.

NEW EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

John H. Gibbon, Jr., M.D.
1025 Walnut Street, Philadelphia 7, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to Dr. Gibbon at the above address.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.

INDEX TO VOLUME 125

A

- ABBOTT, KENNETH H., and CRAIG, WINCHELL McK.: Surgical Considerations in the Treatment of Hypertension, 608.
- ABRAMSON, DAVID I., and SHUMACKER, HARRIS B., JR.: Sympathectomy in Trench Foot, 203.
- Absorbable Alginate Products in Surgery, Experimental Observations on, 102.
- Acid Débridement of Burns, Studies on the, 418.
- Acute Arterial Deficit, Extremity Refrigeration without Tourniquet Ligation in Cases of, 431.
- Adenoma of the Thyroid, Malignant, with Secondary Metastases to Bone, 282.
- Alginate Products, Absorbable, in Surgery, Experimental Observations on, 102.
- ALLBRIGHT, FRANK F., JR.: Simultaneous Repair of Peripheral Nerve and Soft Tissue Defects in the Forearm, 447.
- Ambulation, Early, Wound Disruption and, 768.
- Amputation, Radical, and Bilateral Oophorectomy, Treatment of Cancer of the Breast in Premenopausal Patients with, 703.
- Analysis of Pelvic Operations Preceding Hysterectomy, 669.
- Anastomosis, in Primary Arterial Injuries, War Experiences with the Nonsuture Technic of, 157.
- Anatomic Data Regarding the Surgical Treatment of Angina Pectoris, 49.
- Anesthesia, Spinal, Phenylpropanolamine Hydrochloride, a Vasopressor Drug, for Maintaining Blood Pressure during, 171.
- Angina Pectoris, Anatomic Data Regarding the Surgical Treatment of, 49.
- ANNOUNCEMENT, Editorial Board Changes, 513.
- Arterial Deficit, Acute, Extremity Refrigeration without Tourniquet Ligation in Cases of, 431.
- Arterial Injuries, Primary, War Experiences with the Nonsuture Technic of Anastomosis in, 157.
- Atresia, Esophageal, and Tracheo-esophageal Fistula, 23.
- Autogenous Diced Cartilage Transplants to Bone, 237.

B

- Bacteriologic Study of Burn Wounds, 452
- BAER, RUDOLF L., *et al.*: Studies on the Acid Débridement of Burns, 418.
- BARGEN, J. ARNOLD, *et al.*: Nutritional Rehabilitation of Surgical Patients, 115.
- BARTELS, ELMER C., and LAHEY, FRANK H.: The Use of Thiouracil, Thiobarbital and Propylthiouracil in Patients with Hyperthyroidism, 572.
- BARTLETT, WILLARD: A Concept of Toxic Goiter, 566.
- BAXTER, HAMILTON, and MORE, ROBERT H.: The Effect of the Local Reduction of Temperature on Scald Burns in the Rat, 177.
- BECKER, WALTER F., and LEHMAN, EDWIN P.: The Mortality of Surgical Disease, 515.

- BERRY, ROBERT E. L., *et al.*: Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729.
- Bilateral Cutaneous Ureterostomy Eighteen Years after Ureterosigmoidostomy for Exstrophy of the Bladder, 788.
- Bilateral Oophorectomy, and Radical Amputation, Treatment of Cancer of the Breast in Premenopausal Patients with, 703.
- Bladder, Exstrophy of the, Bilateral Cutaneous Ureterostomy Eighteen Years after Ureterosigmoidostomy for, 788.
- BLAINE, GEORGE: Experimental Observations on Absorbable Alginate Products in Surgery, 102.
- BLALOCK, ALFRED: The Use of Shunt or By-pass Operations in the Treatment of Certain Circulatory Disorders, Including Portal Hypertension and Pulmonic Stenosis, 129.
- Blood Pressure, during Spinal Anesthesia, A Vasopressor Drug, Phenylpropanolamine Hydrochloride, for Maintaining, 171.
- Blood Volume, Reduced, Problem of, in the Chronically Ill Patient: Chronic Shock, 618.
- Bone, Autogenous Diced Cartilage Transplants to, 237; Secondary Metastases to, in Malignant Adenoma of the Thyroid, 282.
- Bone Grafting Methods, 96.
- BOOK REVIEW: Scientific, Medical and Technical Books Published in the United States of America, 1930-1944, Reviewed by Wesley Draper, 128.
- Brachial Plexus, Treatment of Injuries of the, 647.
- BRADLEY, CLOYCE F., and BURCH, JOHN C.: Wound Disruption and Early Ambulation, 768.
- Breast, Carcinoma of the, 673; Results of Combined Treatment with Surgery and Roentgen Therapy, 688; Treatment of Cancer of the, in Premenopausal Patients with Radical Amputation and Bilateral Oophorectomy, 703.
- BURCH, JOHN C., and BRADLEY, CLOYCE F.: Wound Disruption and Early Ambulation, 768.
- Burn Wounds, Bacteriologic Study of, 452; Expeditious Care of Full-thickness, by Surgical Excision and Grafting, 1.
- Burns, Scald, in the Rat, Effect of the Local Reduction of Temperature on, 177; Studies on the Acid Débridement of, 418.
- BURNS, EOGAR, *et al.*: Bilateral Cutaneous Ureterostomy Eighteen Years after Ureterosigmoidostomy for Exstrophy of the Bladder, 788.
- By-pass, or shunt operations, Use of, in the Treatment of Certain Circulatory Disorders, Including Portal Hypertension and Pulmonic Stenosis, 129.

C

- CAMPBELL, KENNETH N., *et al.*: Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729.

Cancer of the Breast, Treatment of, in Premenopausal Patients with Radical Amputation and Bilateral Oophorectomy, 703

Carcinoma of the Breast, 673, Results of Combined Treatment with Surgery and Roentgen Therapy, 688, Experimental, of the Gallbladder, 241, of the Lip, Should the Neck Nodes be Dissected in Patients with?, 658, of the Lung, Present Status of the Surgical Treatment of, 541, Perforated, of the Large Intestine Complicating Pregnancy, 251

Care Expeditions, of Full thickness Burn Wounds by Surgical Excision and Grafting, 1

Cartilage Transplants to Bone, Autogenous Diced, 237

CAVE, EDWIN F., and ROWE, CARTER R. Utilization of Skin from Deformed and Useless Fingers to Cover Defects in the Hand, 126

Celiotomy, Large Melena Caused by Sponge Ulcerating into Lumen of Ileum more than Twenty Years after, 249

Cells, Malignant, Study of, with Phase Difference Microscopy, 604

Cerebrospinal, Spontaneous Rhinorrhea, the Surgical Treatment of, 718

Chronic Shock The Problem of Reduced Blood Volume in the Chronically Ill Patient, 618

Chronically Ill Patient, Problem of Reduced Blood Volume in the, Chronic Shock, 618

Circulatory Disorders, Including Portal Hypertension and Pulmonic Stenosis, The Use of Shunt or Bypass Operations in the Treatment of certain, 129

CLARK, JOHN H., *et al* Chronic Shock The Problem of Reduced Blood Volume in the Chronically Ill Patient, 618

Closure, Wound, without the Use of Grafts 779

COLEMAN, CLAUDE C., and TROLAND, CHARLES E. The Surgical Treatment of Spontaneous Cerebrospinal Rhinorrhea, 718

COLLER, FREDERICK A., *et al* Tetra ethyl ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729

COLONNA, PAUL C. Bone Grafting Methods, 96

Combined Treatment with Surgery and Roentgen Therapy, Results of Carcinoma of the Breast, 688.

Complications, Late, Surgical Management of Gunshot Wounds of the Pelvic Viscera and Their, 399

Compound Injuries of the Knee Joint, Study I, 341 Study II The Infected Knee Joint, 385

Concept of Toxic Goiter, 566

Congenital Dislocation of the Hip, 216

COPE, OLIVER, *et al* Expeditious Care of Full thickness Burn Wounds by Surgical Excision and Grafting, 1, Bacteriologic Study of Burn Wounds, 452

CRAIG, WINCHELL MCK., and ABBOTT, KENNETH H.: Surgical Considerations in the Treatment of Hypertension, 608

CROCE, EDMUND J. and POTTER, STANLEY E. The Treatment of Peripheral Nerve Injuries Complicated by Skin and Soft Tissue Defects, 349.

CURTIS, GEORGE M., *et al* The Surgical Therapeutic Significance of the Functional Behavior of Thyroid Nodules, 257

D

Dati, Anatomie, Regarding the Surgical Treatment of Angina Pectoris, 49

DAVIS, LOYAL, *et al* The Treatment of Injuries of the Brachial Plexus, 647

DIBAKKY, MICHAEL, *et al* Primary Pulmonary Malignancy Treated by Resection, 522

Debridement, Acid, of Burns, Studies on the, 418

DICAMP, PAUL, *et al* Chronic Shock The Problem of Reduced Blood Volume in the Chronically Ill Patient, 618

Defects in the Hand, Utilization of Skin from Deformed and Useless Fingers to Cover, 126, Skin and Soft Tissue, Treatment of Peripheral Nerve Injuries Complicated by, 349, Soft Tissue and Peripheral Nerve, Simultaneous Repair of, in the Forearm, 147

Deformed and Useless Fingers, Utilization of Skin from, to Cover Defects in the Hand 126

Dislocation, Congenital, of the Hip, 216

Diverticulum, Pulsion, of the Pharyngo esophageal Junction Technique of the One stage Operation, 41

DIXON, LEONARD, *et al* Primary Pulmonary Malignancy Treated by Resection, 522

Drug, a Vasopressor, Phenylpropanolamine Hydrochloride, for Maintaining Blood Pressure during Spinal Anesthesia, 171

E

Early Ambulation, Wound Disruption and, 768

Effect of the Local Reduction of Temperature on Scald Burns in the Rat, 177

ELIASON, E. L., and WELTY, ROBERT F. A Ten year Survey of Intestinal Obstruction 57

Embolism, Pulmonary, an Evaluation of following Intravascular Venous Thrombosis 590

Eosinophilic Solitary Granuloma of Rib, 510

Esophageal Atresia and Tracheo esophageal Fistula, 23

Evaluation of Pulmonary Embolism following Intravascular Venous Thrombosis, 590

Excision, Surgical, and Grafting, Expeditious Care of Full thickness Burn Wounds by 1

Expeditious Care of Full thickness Burn Wounds by Surgical Excision and Grafting 1

Experiences, War, with the Nonsuture Technique of Anastomosis in Primary Arterial Injuries, 157, with Posttraumatic Osteomyelitis in World War II, 89, with Sympathectomy for Sequelae of Trench Feet, 505

Experimental Carcinoma of the Gallbladder 241, Observations on Absorbable Alginate Products in Surgery, 102

Extremity Refrigeration without Tourniquet Ligation in Cases of Acute Arterial Deficit, 431

Exstrophy of the Bladder, Bilateral Cutaneous Ureterostomy Eighteen Years after Uretero sigmoidostomy for, 788

F

- Fibrosarcoma, Primary, of the Liver, 439.
Fingers, Utilization of Skin from Deformed and Useless, to Cover Defects in the Hand, 126.
FINNEY, GEORGE C., *et al.*: Carcinoma of the Breast, 673.
FIROR, W. M., and GEY, G. O.: The Study of Malignant Cells with Phase Difference Microscopy, 604.
Fistula, Tracheo-esophageal, Esophageal Atresia and, 23.
Forearm, Simultaneous Repair of Peripheral Nerve and Soft Tissue Defects in the, 447.
Full-thickness Burn Wounds, Expeditious Care of, by Surgical Excision and Grafting, 1.
Functional Behavior of Thyroid Nodules, Surgical Therapeutic Significance of the, 257.

G

- Gallbladder, Experimental Carcinoma of the, 241.
GEY, G. O., and FIROR, W. M.: The Study of Malignant Cells with Phase Difference Microscopy, 604.
GLENN, FRANK: The Surgical Treatment of 1,545 Herniae, 72.
Goiter, Toxic, a Concept of, 566.
GORDON, STUART D., and WARREN, RUPERT F.: Autogenous Diced Cartilage Transplants to Bone, 237.
Grafting, Bone, Methods of, 96; and Surgical Excision, Expeditious Care of Full-thickness Burn Wounds by, 1.
Grafts, Wound Closure without the Use of, 778.
Granuloma, Solitary, Eosinophilic, of Rib, 510.
Gunshot Wounds, of the Pelvic Viscera and Their Late Complications, Surgical Management of, 399.

H

- Hand, Utilization of Skin from Deformed and Useless Fingers, to cover Defects in the, 126.
HARE, HUGH F., and MARSHALL, SAMUEL E.: Carcinoma of the Breast: Results of Combined Treatment with Surgery and Roentgen Therapy, 688.
HARRISON, ALBERT W., and MISCALL, LAURENCE: Thoracic Surgery in a Hospital Center, Part I, 142; Part II, 311.
HARTMAN, J. C., *et al.*: Perforated Carcinoma of the Large Intestine Complicating Pregnancy, 251.
Hemostasis, Mechanism of, 292.
Herniae, Surgical Treatment of 1,545, 72.
Hip, Congenital Dislocation of the, 216.
HODGE, IAN G., and SANDERS, GEORGE BENTON: Surgical Management of Gunshot Wounds of the Pelvic Viscera and Their Late Complications, 399.
HORSLEY, GUY W.: Treatment of Cancer of the Breast in Premenopausal Patients with Radical Amputation and Bilateral Oophorectomy, 793.
HOWORTH, M. BECKETTS, Congenital Dislocation of the Hip, 216.

- Hospital Center, Thoracic Surgery in a, Part I, 142; Part II, 311.
Hydrochloride, Phenylpropanolamine: A Vaso-pressor Drug, for Maintaining Blood Pressure during Spinal Anesthesia, 171.
HYMAN, JACK, *et al.*: Bilateral Cutaneous Ureterostomy Eighteen Years after Ureterosigmoidostomy for Exstrophy of the Bladder, 788.
Hypertension, Portal, and Pulmonic Stenosis, The Use of Shunt or By-pass Operations in the Treatment of Certain Circulatory Disorders, including, 129; Treatment of, Surgical Considerations in the, 608.
Hypertensive Patients, a Technic for Testing, Preoperatively, 119.
Hyperthyroidism, Use of Thiouracil, Thiobarbital and Propylthiouracil in Patients with, 572.
Hysterectomy, Analysis of Pelvic Operations Preceding, 669; Vaginal, Ligature Carrier for, 508.

I

- Infected Knee Joint (Part II), Compound Injuries of the Knee Joint, 385.
Infections, Surgical, Streptomycin in.: I. Laboratory Studies, 194.
Injuries, Arterial, Primary, War Experiences with the Nonsuture Technic of Anastomosis in, 157; Compound, of the Knee Joint, 341; Compound, of the Knee Joint; II. The Infected Knee Joint, 385; Nerve, Peripheral, Complicated by Skin and Soft Tissue Defects, Treatment of, 349; Treatment of, of the Brachial Plexus, 647.
Intestinal Obstruction, a Ten-year Survey of, 57.
Intestine, large, Perforated Carcinoma of the, Complicating Pregnancy, 251.
Intravascular Venous Thrombosis, An Evaluation of Pulmonary Embolism following, 590.

J

- Joint, Knee, Compound Injuries of the, Part I, 341; Part II, The Infected Knee Joint, 385.
Junction, Pharyngo-esophageal, Pulsion Diverticulum of the: Technic of the One-stage Operation, 41.

K

- KANOF, ABRAM, *et al.*: Studies on the Acid Débridement of Burns, 418.
KITTREDGE, W. E., *et al.*: Bilateral Cutaneous Ureterostomy Eighteen Years after Ureterosigmoidostomy for Extrophy of the Bladder, 788.
KLEMM, ROLAND M., *et al.*: Anatomic Data Regarding the Surgical Treatment of Angina Pectoris, 49.
Knee Joint, Compound Injuries of the, Part I, 341; Part II, The Infected Knee Joint, 385.
Knee Joint, Infected (Part II), Compound Injuries of the Knee Joint, 385.
KRONTRIS, A.: Experiences with Sympathectomy for Sequelae of Trench Feet, 505.

KROTKINA, N. A., and PETROV, N. N.: Experimental Carcinoma of the Gallbladder, 241.

L

Laboratory Studies: Streptomycin in Surgical Infections, 194.

LADD, WILLIAM E., and SWENSON, ORVAR: Esophageal Atresia and Tracheo-esophageal Fistula, 23.

LAHEY, FRANK H., and BARTELS, ELMER C.: The Use of Thiouracil, Thiobarbital and Propylthiouracil in Patients with Hyperthyroidism, 572.

LAM, CONRAD R., and McCCLURE, ROY D.: Should the Neck Nodes be Dissected in Patients with Carcinoma of the Lip?, 658.

LANGOHR, JOHN L., *et al.*: Expeditious Care of Full-thickness Burn Wounds by Surgical Excision and Grafting, 1; Bacteriologic Study of Burn Wounds, 452.

Large Intestine, Perforated Carcinoma of the, Complicating Pregnancy, 251.

Large Melena Caused by Sponge Ulcerating into Lumen of Ileum more than Twenty Years after Celiotomy, 249.

LEBLOND, CHARLES P., *et al.*: The Surgical Therapeutic Significance of the Functional Behavior of Thyroid Nodules, 257.

Le Fort Operation, Modern Technic of the, 334.

Leg Length, Discrepancy Problem, Present Status of the, 662.

LEHMAN, EDWIN P., and BECKER, WALTER F.: The Mortality of Surgical Disease, 515.

Ligation, Tourniquet, Extremity Refrigeration without, in Cases of Acute Arterial Deficit, 431.

Ligature Carrier for Vaginal Hysterectomy, 508.

Lip, Carcinoma of the, Should the Neck Nodes be Dissected in Patients with?, 658.

Liver, Primary Fibrosarcoma of the, 439; Wounds of the, 756.

LIVINGSTON, KENNETH E.: Extremity Refrigeration without Tourniquet Ligation in Cases of Acute Arterial Deficit, 431.

LONG, JOHN C., *et al.*: Experiences with Post-traumatic Osteomyelitis in World War II, 89.

LORHAN, PAUL H., and MOSSER, DONN: Phenylpropanolamine Hydrochloride: A Vasopressor Drug, for Maintaining Blood Pressure during Spinal Anesthesia, 171.

Lumen of Ileum, Large Melena Caused by Sponge Ulcerating into, more than twenty years after Celiotomy, 249.

Lung, Carcinoma of the, Present Status of the Surgical Treatment of, 541.

LYONS, CHAMP, *et al.*: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient, 618.

LYONS, RICHARD H., *et al.*: Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729.

M

MAHONEY, E. B., *et al.*: An Evaluation of Pulmonary Embolism following Intravascular Venous Thrombosis, 590.

Maintaining Blood Pressure During Spinal Anesthesia, Phenylpropanolamine Hydrochloride, A Vasopressor Drug for, 171.

Malignancy, Primary Pulmonary, Treated by Resection, 522.

Malignant Adenoma of the Thyroid, with Secondary Metastases to Bone, 282.

Malignant Cells, Study of, with Phase Difference Microscopy, 604.

Management, Surgical, of Gunshot Wounds of the Pelvic Viscera and Their Late Complications, 399.

MARSHALL, SAMUEL F., and HARE, HUGH F.: Carcinoma of the Breast: Results of Combined Treatment with Surgery and Roentgen Therapy, 688.

MARTIN, J. D., JR.: Wounds of the Liver, 756.

MARTIN JOHN, *et al.*: The Treatment of Injuries of the Brachial Plexus, 647.

MAYERSON, H. S., *et al.*: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient, 618.

McCCLURE, ROY D., and LAM, CONRAD R.: Should the Neck Nodes be Dissected in Patients with Carcinoma of the Lip?, 658.

McNEER, GORDON, *et al.*: Experiences with Post-traumatic Osteomyelitis in World War II, 89.

Mechanism of Hemostasis, The, 292.

Melena, large, Caused by Sponge Ulcerating into Lumen of Ileum more than Twenty Years after Celiotomy, 249.

MERKEL, WALTER C., *et al.*: Carcinoma of the Breast, 673.

Metastases to Bone, Secondary, in Malignant Adenoma of the Thyroid, 282.

Methods, Bone Grafting, 96.

Microscopy, Phase Difference, The Study of Malignant Cells with, 604.

MIDER, G. B., *et al.*: An Evaluation of Pulmonary Embolism following Intravascular Venous Thrombosis, 590.

MILLER, DONALD B., *et al.*: Carcinoma of the Breast, 673.

MISCALL, LAURENCE, and HARRISON, ALBERT W.: Thoracic Surgery in a Hospital Center, Part I, 142; Part II, 311.

Modern Technic of the Le Fort Operation, The, 334.

MODLIN, JOHN J. and PARKER, JOE M.: Compound Injuries of the Knee Joint. Study I, 341; Study II, The Infected Knee Joint, 385.

MOE, GORDON K., *et al.*: Tetra-ethyl ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729.

MOORE, FRANCIS D., *et al.*: Expeditious Care of Full-thickness Burn Wounds by Surgical Excision and Grafting, 1.

MORE, ROBERT H., and BAXTER, HAMILTON: The Effect of the Local Reduction of Temperature on Scald Burns in the Rat, 177.

Mortality of Surgical Disease, 515.

MORTON, JOHN J., *et al.*: An Evaluation of Pulmonary Embolism following Intravascular Venous Thrombosis, 590.

MOSSE, DONN, and LORHAN, PAUL H.: Phenylpropanolamine Hydrochloride: A Vasopressor Drug, for Maintaining Blood Pressure during Spinal Anesthesia, 171.

N

- Neck Nodes, Should they be Dissected in Patients with Carcinoma of the Lip?, 658.
- NELSON, WOODROW, *et al.*: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient, 618.
- Nerve Injuries, Peripheral, Complicated by Skin and Soft Tissue Defects, Treatment of, 349.
- NEWTON, Z. B., *et al.*: Perforated Carcinoma of the Large Intestine Complicating Pregnancy, 251.
- Nodes, Neck, Should they be Dissected, in Patients with Carcinoma of the Lip?, 658.
- Nonsuture technic of Anastomosis, War Experiences with the, in Primary Arterial Injuries, 157.
- Nutritional Rehabilitation of Surgical Patients, 115.

O

- OBITUARIES: Dr. James T. Pilcher, 799; and Dr. George P. Muller, 798.
- Observations, Experimental, on Absorbable Alginate Products in Surgery, 102.
- Obstruction, Intestinal, a Ten-year Survey of, 57.
- OCHSNER, ALTON, *et al.*: Primary Pulmonary Malignancy Treated by Resection, 522.
- One-stage Operation, Technic of the: Pulsion Diverticulum of the Pharyngo-esophageal Junction, 41.
- Oophorectomy, Bilateral, and Radical Amputation, Treatment of Cancer of the Breast in Premenopausal Patients with, 703.
- Operation, Le Fort, Modern Technic of the, 334; One-stage, Technic of the: Pulsion Diverticulum of the Pharyngo-esophageal Junction, 41; Pelvic, Analysis of, Preceding Hysterectomy, 669; Shunt or By-pass, Use of, in the Treatment of Certain Circulatory Disorders Including Portal Hypertension and Pulmonic Stenosis, 129.
- Orthopedic Surgery, Elective, Value of External Skeletal Fixation in, 372.
- Osteomyelitis, Posttraumatic, Experiences with in World War II, 89.
- OTTO, THOMAS O.: Wound Closure without the Use of Grafts, 778.
- OUTERBRIDGE, RALPH E.: Malignant Adenoma of the Thyroid, with Secondary Metastases to Bone, 282.
- OWEN, CORA R., *et al.*: Bacteriologic Study of Burn Wounds, 452.

P

- Pancreatitis, Traumatic, 66.
- PARKER, JOE M. and MODLIN, JOHN J.: Compound Injuries of the Knee Joint. Study I, 341; Study II, The Infected Knee Joint, 385.
- Pelvic Operations, Analysis of, Preceding Hysterectomy, 669.
- Pelvic Viscera, Surgical Management of Gunshot Wounds of the, and Their Late Complications, 399.

- PEMBERTON, JOHN DEJ., *et al.*: Nutritional Rehabilitation of Surgical Patients, 115.
- PENICK, RAWLEY M., JR.: Use of Thyroid Extract with Thiouracil in the Preparation of the Thyrotoxic Patient, 582.
- Perforated Carcinoma of the Large Intestine Complicating Pregnancy, 251.
- Peripheral Nerve and Soft Tissue Defects in the Forearm, Simultaneous Repair of, 447.
- Peripheral Vascular Disease and other Painful States, Treatment of, Tetra-ethyl-ammonium as an Adjuvant in the, 729; Use of Radioactive Sodium in the Study of, 360.
- PERRET, GEORGE, *et al.*: The Treatment of Injuries of the Brachial Plexus, 647.
- PETROV, N. N., and KROTKINA, N. A.: Experimental Carcinoma of the Gallbladder, 241.
- Pharyngo-esophageal Junction, Pulsion Diverticulum of the: Technic of the One-stage Operation, 41.
- Phase Difference Microscopy, The Study of Malignant Cells with, 604.
- Phenylpropanolamine Hydrochloride: A Vasopressor Drug, for Maintaining Blood Pressure During Spinal Anesthesia, 171.
- Portal Hypertension, and Pulmonic Stenosis, Use of Shunt or By-pass Operations in the Treatment of Certain Circulatory Disorders, Including, 129.
- Posttraumatic Osteomyelitis, Experiences with, in World War II, 89.
- POTTER, STANLEY E. and CROCE, EDMUND J.: The Treatment of Peripheral Nerve Injuries Complicated by Skin and Soft Tissue Defects, 349.
- Pregnancy, Perforated Carcinoma of the Large Intestine Complicating, 251.
- Premenopausal Patients, Treatment of Cancer of the Breast in, with Radical Amputation and Bilateral Oophorectomy, 703.
- Preparation of the Thyrotoxic Patient, Use of Thyroid Extract with Thiouracil in the, 582.
- Present Status of the Leg Length Discrepancy Problem, 662; of the Surgical Treatment of Carcinoma of the Lung, 541.
- Primary Arterial Injuries, War Experiences with the Nonsuture Technic of Anastomosis in, 157; Fibrosarcoma of the Liver, 439; Pulmonary Malignancy Treated by Resection, 522.
- Problem of Reduced Blood Volume in the Chronically Ill Patient: Chronic Shock, 618.
- Propylthiouracil, Thiouracil and Thiobarbital, Use of, in Patients with Hyperthyroidism, 572.
- PULASKI, EDWIN J., and SPRINZ, HELMUTH: Streptomycin in Surgical Infections: I. Laboratory Studies, 194.
- Pulmonary Embolism, an Evaluation of, following Intravascular Venous Thrombosis, 590; Malignancy, Primary, Treated by Resection, 522.
- Pulmonic Stenosis, and Portal Hypertension, Use of Shunt or By-pass Operations in the Treatment of Certain Circulatory Disorders, Including, 129.
- Pulsion Diverticulum of the Pharyngo-esophageal Junction: Technic of the One-stage Operation, 41.
- PUPPEL, I. DARIN, *et al.*: The Surgical Therapeutic Significance of the Functional Behavior of Thyroid Nodules, 257.

Q

- QUINBY, EDITH H., and SMITH, BEVERLY C.:
The Use of Radioactive Sodium in the Study
of Peripheral Vascular Disease, 360.

R

- Radical Amputation, and Bilateral Oophorectomy,
Treatment of Cancer of the Breast in Premeno-
pausal Patients with, 703.
Radioactive Sodium, Use of, in the Study of
Peripheral Vascular Disease, 360.
RAO, JOHN O., and SALTZSTEIN, HARRY C.:
Large Melena Caused by Sponge Ulcerating
into Lumen of Ileum more than Twenty Years
after Celiotomy, 249.
Rat, Scald Burns in the, Effect of the Local
Reduction of Temperature on, 177.
Reduced Blood Volume, Problem of, in the
Chronically Ill Patient: Chronic Shock, 618.
Reduction of Temperature, Effect of the Local,
on Scald Burns in the Rat, 177.
Refrigeration, Extremity, without Tourniquet
Ligation in Cases of Acute Arterial Deficit, 431.
Rehabilitation, Nutritional, of Surgical Patients,
115.
REMINGTON, JOHN H., *et al.*: Nutritional Reha-
bilitation of Surgical Patients, 115.
Repair, Simultaneous, of Peripheral Nerve and
Soft Tissue Defects in the Forearm, 447.
Resection, Primary Pulmonary Malignancy
Treated by, 522.
Results of Combined Treatment with Surgery
and Roentgen Therapy: Carcinoma of the
Breast, 688.
Rhinorrhea, Spontaneous Cerebrospinal, the Sur-
gical Treatment of, 718.
Rib, Solitary Eosinophilic Granuloma of, 510.
RIENHOFF, WILLIAM F., JR.: The Present Status
of the Surgical Treatment of Carcinoma of the
Lung, 541.
Roentgen Therapy, and Surgery, Results of Com-
bined Treatment with: Carcinoma of the Breast,
688.
ROWE, CARTER R., and CAVE, ERWIN F.: Utiliza-
tion of Skin from Deformed and Useless Fin-
gers to Cover Defects in the Hand, 126.
RUSSEK, HENRY I., and SOUTHWORTH, JAMES L.:
A Technic for Testing Hypertensive Patients
Preoperatively, 119.

S

- SACCOMANNO, GENO, *et al.*: Anatomic Data Re-
garding the Surgical Treatment of Angina Pec-
toris, 49.
SALTZSTEIN, HARRY C., and RAO, JOHN O.: Large
Melena Caused by Sponge Ulcerating into Lu-
men of Ileum more than Twenty Years after
Celiotomy, 249.
SANDERS, GEORGE BENTON, and HODGE, IAN G.:
Surgical Management of Gunshot Wounds of
the Pelvic Viscera and Their Late Complica-
tions, 399.

- Scald Burns, in the Rat, Effect of the Local
Reduction of Temperature on, 177.
Scalenotomy, 80.
SCHEMAN, L., and SHAFIROFF, B. G. P.: Solitary
Eosinophilic Granuloma of Rib, 510.
Sequelae of Trench Feet, Experiences with Sym-
pathectomy for, 505.
SHAFIROFF, B. G. P., and SCHEMAN L.: Solitary
Eosinophilic Granuloma of Rib, 510.
SHALLOW, THOMAS A., and WAGNER, FREDERICK
B., JR.: Traumatic Pancreatitis, 66; Primary
Fibrosarcoma of the Liver, 439.
Shock, Chronic: The Problem of Reduced Blood
Volume in the Chronically Ill Patient, 618.
Should the Neck Nodes be Dissected in Patients
with Carcinoma of the Lip?, 658.
SHUMACKER, HARRIS B., JR., and ABRAMSON,
DAVID I.: Sympathectomy in Trench Foot, 203.
Shunt, or By-pass Operations, Use of, in the
Treatment of Certain Circulatory Disorders,
Including Portal Hypertension and Pulmonic
Stenosis, 129.
Simultaneous Repair of Peripheral Nerve and
Soft Tissue Defects in the Forearm, 447.
Skeletal Fixation, External, Value of in Elective
Orthopedic Surgery, 372.
Skin and Soft Tissue Defects, Treatment of
Peripheral Nerve Injuries Complicated by, 349;
Utilization of, from Deformed and Useless
Fingers to Cover Defects in the Hand, 126.
SMITH, BEVERLY C. and QUINBY, EDITH H.:
The Use of Radioactive Sodium in the Study
of Peripheral Vascular Disease, 360.
Sodium, Radioactive, Use of, in the Study of
Peripheral Vascular Disease, 360.
Soft Tissue and Peripheral Nerve Defects in the
Forearm, Simultaneous Repair of, 447.
Solitary Eosinophilic Granuloma of Rib, 510.
SOUTHWORTH, JAMES L., and RUSSEK, HENRY I.:
A Technic for Testing Hypertensive Patients
Preoperatively, 119.
Spinal Anesthesia, Phenylpropanolamine Hydro-
chloride, a Vasopressor Drug, for Maintaining
Blood Pressure during, 171.
Sponge Ulcerating into Lumen of Ileum more
than Twenty Years after Celiotomy, Large
Melena Caused by, 249.
Spontaneous Cerebrospinal Rhinorrhea, Surgical
Treatment of, 718.
SPRINZ, HELMUTH, and PULASKI, EDWIN J.:
Streptomycin in Surgical Infections: I. Labo-
ratory Studies, 194.
STARK, W. J.: The Value of External Skeletal
Fixation in Elective Orthopedic Surgery, 372.
STAYMAN, J. W., JR., *et al.*: Perforated Carcinoma
of the Large Intestine Complicating Pregnancy,
251.
STEIN, HYMEN D., *et al.*: Experiences with
Posttraumatic Osteomyelitis in World War II,
89.
Stenosis, Pulmonic, and Portal Hypertension, the
Use of Shunt or By-pass Operations in the
Treatment of Certain Circulatory Disorders,
Including, 129.
STEWART, CHARLES F.: War Experiences with the
Nonsuture Technic of Anastomosis in Primary
Arterial Injuries, 157.

- Streptomycin in Surgical Infections: Laboratory Studies, 194.
- Studies of the Acid Débridement of Burns, 418; Laboratory; Streptomycin in Surgical Infections, 194.
- Study, Bacteriologic, of Burn Wounds, 452; of Malignant Cells with Phase Difference Microscopy, 604.
- SULZBERGER, MARION B., *et al.*: Studies on the Acid Débridement of Burns, 418.
- Surgery. Experimental Observations on Absorbable Alginate Products in, 102; Orthopedic, Elective, Value of External Skeletal Fixation in, 372; and Roentgen Therapy, Results of Combined Treatment with: Carcinoma of the Breast, 688; Thoracic, in a Hospital Center, Part I, 142; Part II, 311.
- Surgical Considerations in the Treatment of Hypertension, 608; Disease, Mortality of, 515; Excision and Grafting, Expedient Care of Full-thickness Burn Wounds by, 1; Infections, Streptomycin in: I. Laboratory Studies, 194; Management of Gunshot Wounds of the Pelvic Viscera and Their Late Complications, 399; Patients, Nutritional Rehabilitation of, 115; Therapeutic Significance of the Functional Behavior of Thyroid Nodules, 257.
- Surgical Treatment of Angina Pectoris, Anatomic Data Regarding the, 49; of Carcinoma of the Lung, Present Status of the, 541; of 1,545 Herniae, 72; of Spontaneous Cerebrospinal Rhinorrhea, 718.
- Survey, Ten-year, of Intestinal Obstruction, 57.
- SUTLER, MARTIN R., *et al.*: Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729.
- SWARTLEY, W. B., *et al.*: Perforated Carcinoma of the Large Intestine Complicating Pregnancy, 251.
- SWEET, RICHARD H.: Pulsion Diverticulum of the Pharyngo-esophageal Junction: Technic of the One-stage Operation, 41.
- SWENSON, ORVAR, and LADD, WILLIAM E.: Esophageal Atresia and Tracheo-esophageal Fistula, 23.
- Sympathectomy, Experiences with, for Sequelae of Trench Feet, 505; in Trench Foot, 203.

T

- TANNA, JEROME F.: Scalenotomy, 80.
- TAUBER, ROBERT: The Modern Technic of the Le Fort Operation, 334; Ligature Carrier for Vaginal Hysterectomy, 508.
- Technic, Modern, of the Le Fort Operation, 314; of the One-stage Operation: Pulsion Diverticulum of the Pharyngo-esophageal Junction, 41; for Testing Hypertensive Patients Preoperatively, 119.
- Temperature, Effect of the Local Reduction of, on Scald Burns in the Rat, 177.
- Ten-year Survey of Intestinal Obstruction, 57.
- Testing Hypertensive Patients Preoperatively, A Technic for, 119.
- Tetra-ethyl-ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and other Painful States, 729.

- Therapy, Roentgen, and Surgery, Results of Combined Treatment with: Carcinoma of the Breast, 688.
- Thiobarbital, Thiouracil and Propylthiouracil, Use of, in Patients with Hyperthyroidism, 572.
- Thiouracil, Thiobarbital and Propylthiouracil, Use of, in Patients with Hyperthyroidism, 572; Use of Thyroid Extract with, in the Preparation of the Thyrotoxic Patient, 582.
- Thoracic Surgery in A Hospital Center, Part I, 142; Part II, 311.
- Thrombosis, Intravascular Venous, An Evaluation of Pulmonary Embolism following, 590.
- Thyroid Extract, Use of, with Thiouracil in the Preparation of the Thyrotoxic Patient, 582; Malignant Adenoma of, with Secondary Metastases to Bone, 282; Nodules, Functional Behavior of, Surgical Therapeutic Significance of, 257.
- Thyrotoxic Patient, Use of Thyroid Extract with Thiouracil in the Preparation of the, 582.
- TOCANTINS, LEANDRO M.: The Mechanism of Hemostasis, 292.
- Tourniquet Ligation, Extremity Refrigeration without, in Cases of Acute Arterial Deficit, 431.
- Toxic Goiter, a Concept of, 566.
- Tracheo-esophageal Fistula, Esophageal Atresia and, 23.
- Transplants to Bone, Autogenous Diced Cartilage, 237.
- Traumatic Pancreatitis, 66.
- Treatment of Cancer of the Breast in Premenopausal Patients with Radical Amputation and Bilateral Oophorectomy, 703; of Certain Circulatory Disorders, Including Portal Hypertension and Pulmonic Stenosis, the Use of Shunt or By-pass Operations in the, 129; Combined, with Surgery and Roentgen Therapy, Results of: Carcinoma of the Breast, 688; of Hypertension, Surgical Considerations in the, 608; of Injuries of the Brachial Plexus, 647; of Peripheral Nerve Injuries Complicated by Skin and Soft Tissue Defects, 349; of Peripheral Vascular Disease and other Painful States, Tetra-ethyl-ammonium as an Adjunct in the, 729; Surgical, of Angina Pectoris. Anatomic Data Regarding the, 49; of Carcinoma of the Lung, Present Status of the, 541; of 1,545 Herniae, 72; of Spontaneous Cerebrospinal Rhinorrhea, 718.
- Trench Feet, Experiences with Sympathectomy for Sequelae of, 505; Sympathectomy in, 203.
- TROLAND, CHARLES E., and COLEMAN, CLAUDE C.: The Surgical Treatment of Spontaneous Cerebrospinal Rhinorrhea, 718.
- TYRONE, CURTIS: Analysis of Pelvic Operations Preceding Hysterectomy, 669.

U

- Ureterosigmoidostomy, Bilateral Cutaneous Ureterostomy Eighteen Years after, for Exstrophy of the Bladder, 788.
- Ureterostomy. Bilateral Cutaneous, Eighteen Years after Ureterosigmoidostomy for Exstrophy of the Bladder, 788.

- Use of Grafts, Wound Closure without the, 778.
Radioactive Sodium in the Study of Peripheral Vascular Disease, 360; Shunt or By-Pass Operations in the Treatment of Certain Circulatory Disorders, Including Portal Hypertension and Pulmonic Stenosis, 129; Thiouracil, Thiobarbital and Propylthiouracil in Patients with Hyperthyroidism, 572; Thyroid Extract with Thiouracil in the Preparation of the Thyrotoxic Patient, 582.
Utilization of Skin from Deformed and Useless Fingers to Cover Defects in the Hand, 126.
UTTERBACK, ROBERT A., *et al.*: Anatomic Data Regarding the Surgical Treatment of Angina Pectoris, 49.

V

- Vaginal Hysterectomy, Ligature Carrier for, 508.
Value of External Skeletal Fixation in Elective Orthopedic Surgery, 372.
Vascular Disease, Peripheral, and other Painful States, Tetra-ethyl-ammonium as an Adjunct in the Treatment of, 729; Use of Radioactive Sodium in the Study of, 360.
Vasopressor Drug, Phenylpropanolamine Hydrochloride, for Maintaining Blood Pressure during Spinal Anesthesia, 171.
Venous Thrombosis, Intravascular, An Evaluation of Pulmonary Embolism following, 590.

W

- WAGNER, FREDERICK B., JR., and SHALLOW, THOMAS A.: Traumatic Pancreatitis, 66; Primary Fibrosarcoma of the Liver, 439.
War Experiences with the Nonsuture Technic of Anastomosis in Primary Arterial Injuries, 157.
WARREN, RUPERT F., and GORON, STUART D.: Autogenous Diced Cartilage Transplants to Bone, 237.
WEBSTER, RICHARD C., JR., *et al.*: Expeditious Care of Full-thickness Burn Wounds by Surgical Excision and Grafting, 1.
WHENIN, WILLIS M., *et al.*: Experiences with Posttraumatic Osteomyelitis in World War II, 89.
WELTY, ROBERT F., and ELIASON E. L.: A Ten-year Survey of Intestinal Obstruction, 57.
WHITE, J. WARREN: The Present Status of the Leg Length Discrepancy Problem, 662.
World War II, Experiences with Posttraumatic Osteomyelitis in, 89.
Wound Closure without the Use of Grafts, 778. Disruption and Early Ambulation, 768.
Wounds, Burn, Bacteriologic Study of, 452; Gunshot, of the Pelvic Viscera and Their Late Complications, Surgical Management of, 399; of the Liver, 756.

